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LESIONS OF THE CEREBRAL HEMISPHERES AND THEIR EFFECTS UPON OPTOKINETIC AND CALORIC NYSTAGMUS

BY

E. A. CARMICHAEL[1], M. R. DIX[2] AND C. S. HALLPIKE[2]

IN 1923 Dusser de Barenne and de Kleyn demonstrated that removal of one cerebral hemisphere in the rabbit led to a central facilitation of induced vestibular nystagmus with its rapid component towards the side of the ablation.

These findings were later confirmed and extended in a study of human subjects by Fitzgerald and Hallpike (1942), who found a similar directional preponderance of caloric nystagmus to the side of the lesion in a number of cases of unilateral cerebral tumour, and were able, in addition, to assign to the temporal lobe the locus of the mechanism responsible for this disturbance.

They further suggested that this effect of temporal lobe lesions was due to a disturbance of a controlling action normally exerted by the temporal lobes upon the reflex responses of the lower vestibular centres. The findings provided an interesting subject for comparison with the earlier demonstration of Fox and Holmes (1926) that unilateral cerebral lesions may bring about a type of asymmetry of optokinetic nystagmus which also amounts, in effect, to a preponderance of the responses towards the side of the lesion.

With a view, therefore, to elucidating the possible relationship between the cerebral nervous mechanisms responsible for directional preponderance to the side of the lesion of caloric and optokinetic nystagmus, two of us (M. R. D. and C. S. H.) have, since 1946, carried out systematic observations at Queen Square upon a series of subjects. In many of these the

[1] From the Neurological Research Unit, Medical Research Council, National Hospital, Queen Square, London, W.C.1.

[2] From the Otological Research Unit, Medical Research Council, National Hospital, Queen Square, London, W.C.1.

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existence of a supratentorial lesion was either evident upon clinical grounds, or was later demonstrated at operation or post-mortem.

The theoretical considerations underlying this investigation, together with the evidence and conclusions derived therefrom, have already been described (Dix and Hallpike, 1951*a* and *b*) and will here be briefly reviewed.

The Neural Mechanisms of Optokinetic Nystagmus

For much of our knowledge of this subject we are indebted to animal experimental studies. The publications of Smith and Bridgman (1943) are particularly clear, and make it evident that optokinetic nystagmus is essentially a brain-stem reflex dependent upon direct nervous pathways from the optic tracts to the superior colliculi and eye muscle nuclei. If these are preserved, then optokinetic nystagmus may be induced following removal of the hemispheres, provided only that the visual stimulus involves a large part of the retina. If, however, the stimulus is a small one, presented upon a large stationary background, then in most animals the nystagmic responses can be obtained only if the cerebral cortex is present.

Largely on the basis of these facts Rademaker and ter Braak (1948) have described two distinct varieties of optokinetic nystagmus. These they define as follows:

"(1) Subcortical optic nystagmus, which occurs when all parts of the visual environment are moving in the same direction.

"(2) Cerebral optic nystagmus, which occurs when successive moving objects which arouse the instinctive 'interest' traverse the field of vision."

The authors' insistence that cerebral optokinetic nystagmus requires a stimulus object of psychic interest would appear capable of misinterpretation. Thus, in the normal human subject optokinetic nystagmus may be induced with a very small striped revolving drum set in a fixed field, provided only that the subject can be persuaded to maintain fixation on the stripes. The moment this fixation is relaxed the nystagmus ceases. Thus it would seem more correct to say that macular fixation involving attention is the essential factor in the mechanism of this so-called cerebral optokinetic nystagmus. Naturally enough in animals such fixation upon a small moving object can only be ensured if this latter is of psychic interest; nevertheless psychic interest *per se* does not play a part.

It seems clear that in our own investigation we have been concerned chiefly with the cerebral type of optokinetic nystagmus, of which the neutral mechanism has been closely investigated by Stenvers (1926), Cords (1926) and others. Their findings have been critically reviewed by Carmichael (1927).

Cords's explanation of the nervous pathways which subserve this mechanism is of particular value, and is shown in fig. 1 which represents the pathways for optokinetic nystagmus to the left, i.e. with its rapid component to the left. From the right halves of the retinæ fibres pass

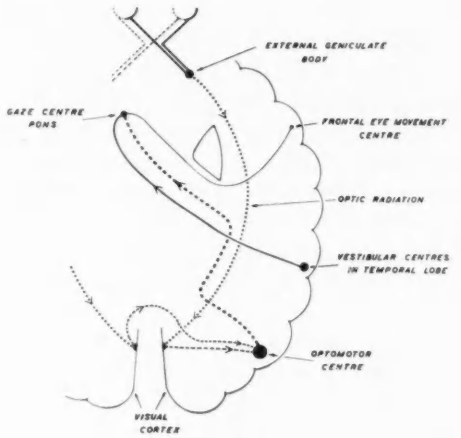

FIG. 1.

via the right external geniculate body, optic radiation and visual cortex to an optomotor centre situated in the peristriate cortex corresponding to Brodman's area No. 18. Other authors, however, place this optomotor area in the angular gyrus. Wherever it is placed, it should be noted that it receives fibres, not only from the visual cortex of the same side, but also from that of the opposite side by way of the corpus callosum. From the optomotor centre, fibres pass to the deeper aspect of the optic radiation in its posterior part and pass forward with it. They part company with the optic radiation at its anterior third, pass into the cerebral peduncle, cross the mid-line, and enter the posterior longitudinal bundle of the opposite side, along which they pass to the centre for conjugate eye movements in the pons, the so-called gaze centre. A lesion anywhere along the path from the optomotor centre to the gaze centre will abolish optokinetic nystagmus to the left. If the lesion occurs on that part of the optomotor pathway in which this is associated with the optic radiation, that is in its posterior two-thirds, then the optokinetic paralysis will be associated with an homonymous hemianopia. If, however, the lesion of the optomotor pathway occurs elsewhere, in the centre itself or further down in the brain-stem, then optokinetic paralysis will occur alone.

The Nature and Relationship of the Brain-stem Mechanism of Vestibular and Optokinetic Nystagmus

The neuro-anatomy of the optokinetic and vestibular pathways within the brain-stem and their relationship to the vestibular centres is particularly relevant to the present studies. Thus Ohm (1922) in an extensive series of investigations, has stressed the fact that both vestibular and optokinetic nystagmus exhibit the same rhythmic alternating slow and rapid components, and considers this an indication that both must depend upon some common anatomical mechanism. This he was able to support experimentally by means of his demonstrations that nystagmogenic stimuli, simultaneously applied to the retinæ and labyrinths, cause nystagmus which exhibits a particularly smooth summation of its optokinetic and labyrinthine elements.

In one of his later papers Ohm (1936) claims to have identified the nervous mechanism common to the two responses within the vestibular nuclei themselves, a view which has lately been controverted by the demonstration that in cases of severe streptomycin intoxication with abolition of both caloric and galvanic responses, involving in all probability some organic derangement of the vestibular nuclei, the optokinetic responses remain entirely unaffected.

This finding by Dix, Hallpike and Harrison (1949) led them to postulate that the supratentorial connexions of the optokinetic mechanism passed to the eye muscles via the superior colliculus, by pathways which were entirely separate from the vestibular nuclei and might possibly involve a gaze centre which was independent of that which subserves vestibular nystagmus. The mechanism suggested by Ohm is shown in fig. 2A. The arrangement suggested by Dix, Hallpike and Harrison is shown in fig. 2B.

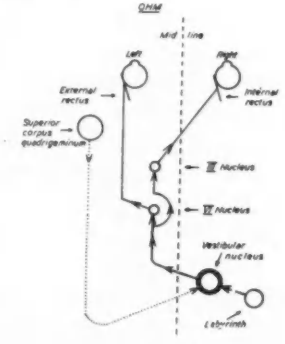

FIG. 2A.

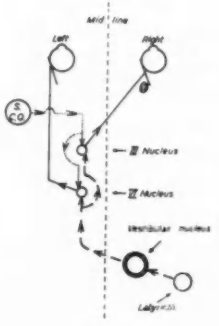

FIG. 2B.

The Anatomical Basis of the Temporal Lobe Influence upon Induced Vestibular Nystagmus

In fig. 1 a pathway has been incorporated from the vestibular centres thought by Fitzgerald and Hallpike to exist in the temporal lobe. This is shown passing to the gaze centre in the pons which also receives impulses from the vestibular nuclei.

It will therefore be seen that in the postero-inferior part of the right cerebral cortex we have supposed to exist not one but two mechanisms, the abolition of either of which can bring about preponderance to the right of induced nystagmus. The clinical and neuro-anatomical basis of the optokinetic mechanism seems fairly well substantiated. Much less information is available, however, concerning the anatomical basis of the vestibular mechanism, and it is necessary to consider whether or not the directional preponderance of induced vestibular nystagmus, observed by Fitzgerald and Hallpike, might be due, not to the disturbance of any specific vestibular centres in the temporal cortex, but rather to an associated disturbance of the optokinetic mechanism which is situated so near to this point. The evidence obtained by Dix and Hallpike (1951 *a* and *b*) upon this question has been of two kinds, both indicating an anatomical independence of the two mechanisms. Firstly, they have pointed out certain intrinsic peculiarities of the directional preponderance of induced vestibular nystagmus due to a temporal lobe lesion which distinguish it from preponderance of optokinetic nystagmus. Thus the directional preponderance of vestibular nystagmus takes the form of prolongation towards the side of the affected temporal lobe without affecting the response to the healthy side. With optokinetic preponderance, however, the reverse is the case; that is to say, the nystagmus to the healthy side is suppressed while that to the affected side appears to be normal. This is, in fact, the way in which Fox and Holmes (1926) described the phenomenon.

Another line of evidence which suggests the anatomical independence of the two mechanisms has been the finding that in a number of instances the two disturbances occur independently of each other; that is to say, normal vestibular nystagmus sometimes occurs with a directional preponderance of optokinetic nystagmus. In others, on the other hand, directional preponderance of vestibular nystagmus may occur with normal optokinetic nystagmus.

In the present paper these findings have been reviewed and subjected to a closer neurological analysis with the particular purpose of establishing the independent existence and topography of the two mechanisms within the cerebral hemisphere.

Methods of Investigation

(1) *Caloric nystagmus.*—For the purpose of this investigation vestibular effects have been measured by means of the caloric method of stimulation of the external canal with quantitative standardization of the stimulus strength as described by Fitzgerald and Hallpike (1942). A two-pint metal douche can is filled with water of which the temperature is adjusted at first to 30° C. and then to 44° C.; i.e. 7° below and above body temperature. The water level is some 60 cm. above the ear to be tested, and is conveyed to it through rubber tubing connected to an ebonite cannula of 4 mm. internal diameter, inserted in the external auditory meatus. The subject lies in the dorsal position for the test with the head raised 30 degrees above the horizontal and fixes his gaze on some convenient point in the ceiling in the centre of his field. Frenzel's glasses or other means for abolishing fixation are not used. Each ear is irrigated in succession, first with water at 30° C, then at 44° C. The stimulus period of 40 seconds is measured by a stop watch and precautions are taken to ensure that the minimum volume of water reaching the ear during this period is not less than 300 c.c. Reaction duration is measured from the beginning of the irrigation to the point of disappearance of the nystagmus which is closely observed under good illumination at a distance of 10 in. The results are recorded graphically, as shown in fig. 3, which depicts a normal reaction pattern. Each con-

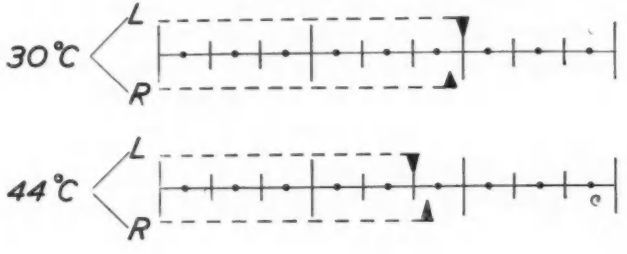

Fig. 3.

tinuous line represents a three-minute interval. The nystagmus durations are denoted by the interrupted lines.

The four reactions shown may be referred to by Nos. 1 to 4 from above downwards.

In fig. 4 are illustrated the caloric reaction patterns in cerebral lesions affecting the temporal lobe, in which caloric nystagmus directed towards the affected side is increased. The responses on the right show directional preponderance to the left, i.e. exaggeration of reactions 2 and 3 with respect to reactions 1 and 4. The responses on the left show directional preponderance to the right, i.e. exaggeration of reactions 1 and 4 with respect to reactions 2 and 3.

A statistical study of the caloric test results obtained in a series of normal subjects was published in 1951 by Hallpike, Harrison and

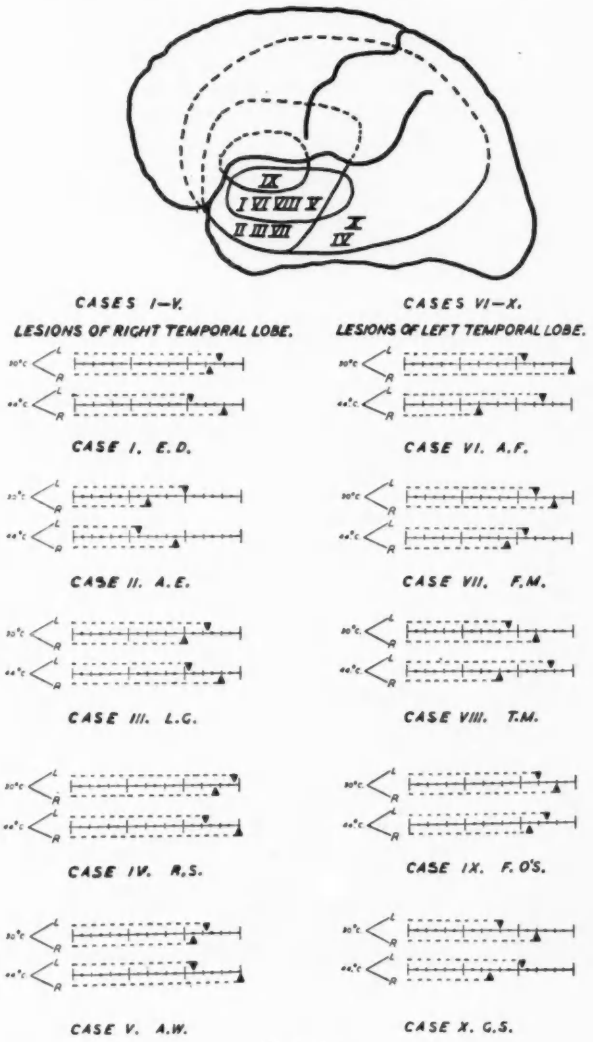

FIG. 4.

Slater and provided the basis for the interpretation of the results obtained in the present investigation. In respect of directional preponderance the authors obtained a frequency distribution curve of Gaussian form with a mean value of 0 and a satisfactorily small standard deviation (15 sec.). These findings have since been confirmed by the further statistical studies of Petermann (1953) and Thomsen (1953).

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(2) *Optokinetic nystagmus.*—The responses obtained were presumed to be dependent upon the cortical optokinetic mechanism and a small drum was used, thus limiting the area of the retina stimulated. The physical characteristics of the stimulus may be derived from the following description of the drum.

This consisted of a Duralumin cylinder, 30 cm. in length and 15 cm. in diameter. Its axis could be fixed in any position according to the plane of the nystagmus which it was desired to elicit.

In the course of the present investigations the axis was vertical. The speed of rotation was controlled by means of a three-speed gear box. The three speeds provided were 360°/sec, 180°/sec. and 72°/sec. A reversing switch was also incorporated. Both the speed control and the reversing switch could be operated instantaneously by the examiner without relaxing his scrutiny of the subject's eyes. In this way very fine judgments of directional preponderance of the nystagmic responses were made possible. The drum was viewed by the subject from a distance of about 50 cm. The general arrangement of subject, examiner and drum is shown in fig. 5.

FIG. 5.

Upon the white surface of the drum and parallel to its axis were inscribed five equidistant black lines each 2 cm. in width. With this arrangement, two lines were always within the subject's field. The translational speeds of the lines, which constituted the visual stimuli across the subject's visual fields, could be calculated geometrically in the manner shown in fig. 6.

D is the drum seen in plan revolving towards the subject's left. The subject's eye is shown at E. The diameter of the drum y–y′ subtends an angle of 17 degrees at the eye. The numerals 1–5 are the lines upon the drum. Each line moves with uniform angular velocity, and hence its circular path projected upon the diameter of the drum

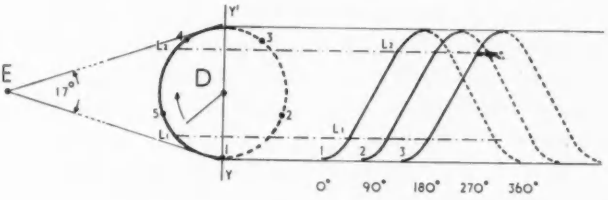

FIG. 6.

takes the approximate form of a simple harmonic motion. Thus the displacements with respect to point y of the lines 1, 2 and 3 during the course of one complete revolution of the drum are represented by the successive sine waves 1, 2 and 3 on the right of the figure.

It will be noted that during the passage of the lines across the central parts of the visual field, i.e. between the points L_1 and L_2 their velocity is approximately linear.

This linear character of the visual stimulus is shown in fig. 7, together with an optical recording of the induced nystagmic response.

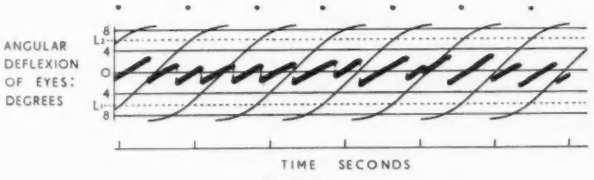

FIG. 7.

The record was obtained by means of an ophthalmograph, an instrument designed and constructed by the American Optical Company for the recording of the fine eye movements which occur in reading.

We have substituted the optokinetic drum for the typescript normally used to evoke the eye movements, and have secured additional rigidity by the use of a dental fixation device. Calibration showed that the deflections which appear upon the record were proportional to the angular deflections of the eye within the range investigated of 8 degrees to the left or right.

The record shows a typical nystagmic response with a drum speed of 72°/sec. The direction of rotation and of the slow component of the nystagmus was to the subject's left.

The angular deflections of the eye, which correspond to the points L_1 and L_2 upon the periphery of the drum, are marked upon the scale of deflections shown upon the left. The passage of the lines upon the drum across the point L was signalled and appears on the record as a series of dots. Using these dots as reference points, the course of each line across the visual field was calculated and inscribed upon the record. Their approximately linear course between the points L_1 and L_2 is well shown.

A point clearly shown in the record is that the speed of the slow component of the nystagmus lags appreciably behind that of the stimulus. Both are approximately linear.

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Material

The clinical material consisted of 73 subjects, inpatients at the National Hospital, Queen Square. All had undergone full neurological and otological examinations, and in every one a unilateral supratentorial cerebral lesion had been localized. The great majority of these have been divided for purposes of analysis into four groups based upon the results of the caloric and optokinetic tests.

Group I consisted of 34 subjects in whom directional preponderance to the side of the cerebral lesion was present of both caloric and optokinetic nystagmus.

Group II consisted of 19 subjects in whom directional preponderance was absent of both caloric and optokinetic nystagmus.

Group III consisted of 13 subjects in whom directional preponderance was present of caloric nystagmus to the side of the cerebral lesion without directional preponderance of optokinetic nystagmus.

Group IV consisted of 3 subjects in whom directional preponderance was present of optokinetic nystagmus to the side of the cerebral lesion. Directional preponderance of caloric nystagmus, however, was either absent or slight.

Group I.—*Directional Preponderance Present of Both Caloric and Optokinetic Nystagmus*

The finding of preponderance to the side of the cerebral lesion of both caloric and optokinetic nystagmus has been encountered in 34 subjects, in every one of whom it has been possible by one means or another to ascertain the site, extent and nature of the supratentorial lesion. Upon this anatomical basis the 34 subjects have been divided into 3 sub-groups.

Sub-Group 1.—Cysts. Number of Subjects 11

A lesion, thought to be due to occlusion of the middle cerebral artery occurring early in life and resulting in the formation of a cyst communicating with the lateral ventricle has been found in 11 subjects. In 9 of these it has been possible to define accurately the extent of the lesion by direct studies of the hemisphere carried out after its removal for therapeutic purposes. On examination of the ablated hemisphere the gyri, either replaced by the cyst formation, or involved in the scar tissue around the cyst, could be readily identified. The posterior part of the inferior and middle frontal gyri, the lower half or two-thirds of the pre-central and post-central gyri and the supramarginal gyrus were found to be involved in all 9 hemispheres. In addition, the superior temporal gyrus in its entirety and the upper half of the middle temporal gyrus were either replaced by cyst formation or completely disorganized; the same types

of abnormality extended posteriorly towards the occipital lobe to include the angular gyrus. In each of these 9 subjects a hemiplegia of early onset had been associated with fits and behaviour disorder, and encephalography had demonstrated a cyst in the distribution described. The clinical findings in the other 2 subjects of this group, whose hemispheres were not removed, have warranted the diagnosis of a similar regional pathology.

Typical of these 11 subjects is the following:

E. P. (Hosp. No. 22684), a young girl of 20 years, was admitted because of fits uncontrolled by medicine, marked behaviour disturbance and evidence of a hemiplegia of early onset. Her parents reported that at birth she had exhibited respiratory distress, and a few days later they observed that she did not move the left arm and leg. She was late in passing the milestones of early childhood and neither talked nor walked till close on 4 years of age. She was backward at school and at the age of 7 started to have fits, which became frequent and did not respond to medicinal therapy. The fits, ushered in by a sensation in the left hand and forearm, involved only the left arm and leg, both of which became rigid and extended. She became untidy, irritable and quarrelsome; she was not amenable to discipline and kept hours and company which caused anxiety to her parents. She had weakness of the left arm and leg, with considerable poverty of movement of the hand; these limbs were smaller than those of the other side. The tendon reflexes of the left side were increased and the left plantar response was extensor in type. Disturbance of sensation, especially of a discriminatory character, was present on the left side and there was also a left hemianopia. Air encephalography demonstrated the presence of a cyst centred on the right Sylvian fissure. At operation for removal of the right hemisphere a large cyst was found which either replaced or was associated with disorganization of the gyri mentioned above. Following the operation, the number of fits became very greatly reduced and her behaviour showed improvement.

In 5 of the 11 subjects the optokinetic and caloric responses were investigated both before and after hemispherectomy. In none was there any post-operative alteration of the optokinetic responses and in 3 the caloric responses also remained unchanged. In the remaining 2, however, operation was followed by an increase in the directional preponderance of the caloric nystagmus towards the side of the absent hemisphere and, by the appearance of a spontaneous nystagmus, in the same direction.

Hemianopia.—In the subject E. P. and in 7 others, a full examination of the visual fields was carried out before operation. In 7 of these including the patient, E. P., varying degrees of hemianopia were present. In the 8th subject, however, the visual fields were full and there thus appears to be no essential correlation between such field defects and the directional preponderance of optokinetic and caloric nystagmus to the site of the cerebral lesion exhibited by all 11 subjects of this sub-group.

Sub-Group 2.—Widespread Diffuse Pathological Changes. Number of Subjects 16

In these 16 subjects widespread abnormality of 1 hemisphere was diagnosed. Each subject suffered from a hemiplegia of early onset, but com-

monly this was first noticed after an acute illness during the second year of life or later. The clinical signs and symptoms observed in these subjects exhibited a greater variety than was found in the 11 subjects of the preceding sub-group. In none was any cyst found on air encephalography; but in every case the ventricle, including the temporal horn, was definitely dilated on the side of the lesion. In 6 subjects the hemisphere was removed for the purpose of relieving the epilepsy and behaviour disturbance. A study of these hemispheres indicated that scattered throughout them were areas of destruction based on occlusion of small vessels; these areas were limited in a few of the cases to the territory of the middle cerebral artery, while in others they were widespread throughout the territories of all 3 of the main cerebral arteries.

Typical of this sub-group is the following subject:

G. B. (Hosp. No. 30536), a 26-year-old woman, until the age of 11 years developed as a healthy child. She then became severely ill and lay for several weeks in a semicomatose condition. It was observed at this time that she had a severe weakness of the left arm and leg. As she improved, the weakness became less profound but she was left with an evident hemiplegia. Some five years after this illness she developed fits of considerable severity. These were ushered in by an epigastric sensation or a feeling of terror. The left leg then passed into a clonic state and was followed by the left arm. These attacks were rendered less severe and frequent by the administration of barbiturates. The illness had left her intellect affected and she became irritable and subject to temper tantrums. Seen when she was 26 years old, she exhibited a left hemiplegia with small left limbs. The degree of weakness was not marked but any attempt at movement was associated with involuntary movement of an athetoid character. The tendon reflexes on the left side were brisker than those on the right, while the left plantar response was extensor in type. There was a raised threshold to all forms of sensation over the left side, and a well marked left hemianopia was present. Air encephalography showed dilatation of the right ventricle including the right temporal horn.

7 of the 16 subjects of this sub-group were operated upon, hemispherectomy being performed in 6 and frontal lobectomy in 1. In the latter subject and in 5 of the former an otoneurological examination was carried out both before and after the operation. The findings in this important group of 6 subjects will be considered first.

Spontaneous nystagmus.—In 1 of the 6 subjects spontaneous nystagmus to the side of the cerebral lesion was present before and after the operation. In none of the remaining 5 was spontaneous nystagmus present either before or after the operation.

Caloric nystagmus.—In all 6 subjects directional preponderance of the caloric responses persisted following operation. In 3 of these the severity of the preponderance was increased. In 2 others, however, the degree of the preponderance was small both before and after operation.

Optokinetic nystagmus.—In 4 of the 6 subjects directional preponder-

ance of optokinetic nystagmus persisted unchanged following the operation. In 2 other subjects failure of co-operation on the part of the patient prevented a satisfactory pre-operative examination of the optokinetic responses. Following the operation, however, both exhibited marked preponderance of the responses towards the side of the cerebral lesion.

Of the 9 other subjects who were operated upon, 4 exhibited spontaneous nystagmus to the side of the cerebral lesion in addition to a preponderance of caloric and optokinetic nystagmus.

Hemianopia.—This was present before operation in 3 of the 7 subjects who were operated upon and in 2 of the 9 subjects who were not operated upon.

A full analysis of the clinical findings in this sub-group has led us to conclude that the presence or absence of hemianopia is unrelated to the occurrence of spontaneous nystagmus or to the severity of directional preponderance of either caloric or optokinetic nystagmus.

Sub-Group 3.—Local Lesions of Special Pathology: Angiomatosis, etc.
Number of Subjects 7

The lesions found in these 7 subjects differed widely in pathology and extent. They are listed as follows: meningioma, 2 subjects; glioma, 2 subjects; trigemino-cerebral angiomatosis, 1 subject; aneurysm, 1 subject; vascular occlusion, 1 subject. Clinical particulars of 2 of these subjects follow:

J. M. (Hosp. No. 22131), a young girl at 11 years of age, had a subarachnoid hæmorrhage which by arteriography was demonstrated to be associated with an aneurysm of the right middle cerebral artery. An attempt was made to tie off this aneurysm and owing to excessive hæmorrhage the surgeon is reported to have placed a clip on the middle cerebral artery at its origin from the carotid artery. Immediately following this, she developed a profound left hemiplegia which gradually lessened but left her with smaller left limbs and poverty of movement in the left hand. The left tendon reflexes were brisker than the right, and the left plantar response was extensor. There was gross sensory disturbance involving the left side. Careful examination of her fields of vision showed that she had difficulty in readily appreciating an object in her left field. Air encephalography showed that she had a series of cysts, each communicating with the ventricle extending throughout the posterior part of the frontal lobe, the parietal lobe and into the region of the Sylvian fissure. She had, in fact, evidence of destruction of the tissue supplied by the middle cerebral artery, and this included the superior temporal gyrus, the angular and supramarginal gyri.

P. C. (Hosp. No. 34357), an 18-year-old girl, suffered from trigemino-cerebral angiomatosis. The areas of skin supplied by the first and second divisions of the right trigeminal nerve were occupied by a diffuse nævus. She had a left hemiplegia with some slight sensory disturbance and a left hemianopia was present. X-rays of the skull demonstrated calcification in the cortex of the right cerebral hemisphere, most marked in the occipital region but extending into the parietal and temporal lobes. This hemisphere was removed and on examination the gyri on the lateral

surface of the occipital lobe and of the parietal lobe were found to be disorganized and containing deposits of calcium. The superior temporal gyrus was similarly affected, especially posteriorly, whence the damage extended into the angular gyrus.

The site and extent of the lesion in each of these 7 subjects was determined from a description of the operation findings, from analysis of the clinical signs or from a study of post-mortem material. The data were then plotted on a surface chart of the hemisphere and in this way it was made clear that the area of destruction common to all 7 lay in the region of the posterior end of the superior and middle temporal gyri, the supramarginal and the angular gyri. The chart is shown in fig. 8.

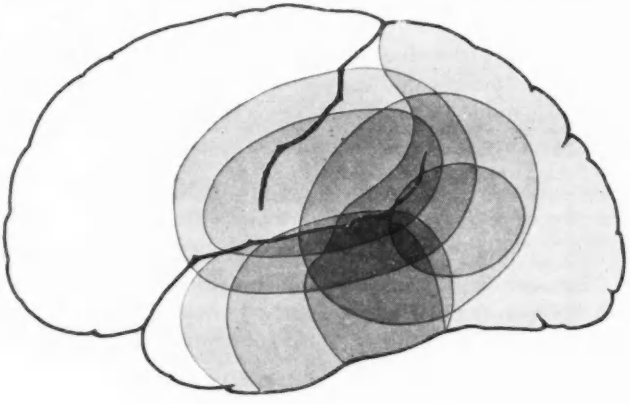

FIG. 8.

The evidence agrees well with that obtained in the subjects of the other 2 sub-groups. Thus, in sub-group 1 the cysts which were demonstrated in the ablated hemisphere were constantly found to involve the gyri mentioned above. The same gyri were also involved by the diffuse changes found to occur in the hemisphere of all the subjects in sub-group 2.

From these observations there would appear to be good reason to conclude that a destructive lesion in the region of these gyri was responsible for the directional preponderance of caloric and optokinetic nystagmus which we have observed in all 34 subjects of Group I.

GROUP II.—*Directional Preponderance Absent of Both Caloric and Optokinetic Nystagmus*

The finding of normal caloric and optokinetic nystagmus has been encountered in 19 subjects; spontaneous nystagmus was absent. In all of these it was possible to establish with accuracy the site, extent and nature of the supratentorial lesions. For clarity of presentation the 19 subjects

will be divided according to the site of the lesions into the following 3 sub-groups: frontal, parietal and temporal.

Sub-Group 1.—Frontal. Number of Subjects 5

In each of these subjects there was unmistakable evidence of a lesion in the frontal lobe. In the first, a tumour was found at operation, in the second there was a history of a vascular incident and clinical examination revealed residual signs of a thrombosis of the anterior frontal branch of the middle cerebral artery. In the third subject, a lad of 10 years, the history and physical findings pointed to the occurrence in early life of an occlusive lesion localized to the frontal lobe. In the remaining 2 subjects epileptic attacks were a prominent feature. The description of these attacks and the presence of spike foci repeatedly demonstrated in the electroencephalogram made clear the existence of frontal lobe abnormality. The following brief notes concern the first of these 5 patients.

D. L. (Hosp. No. 6880), a woman aged 45 years, was admitted because of increasingly severe headaches located mainly in the right frontal region, which had commenced some two or more years previously. In the weeks prior to admission she had been vomiting and had noted deterioration of her vision. She had also become less alert and was suffering from failing memory. On examination no dysphasia was noted. Her fields of vision were full. Neither weakness of movement nor sensory disturbance of any limb was noted. Tendon reflexes were equal on the two sides but the left plantar response was extensor. There was a high grade papilloedema in both eyes. Ventriculography showed an abnormality in the right frontal region due to a space occupying lesion which at operation was found to be a glioma.

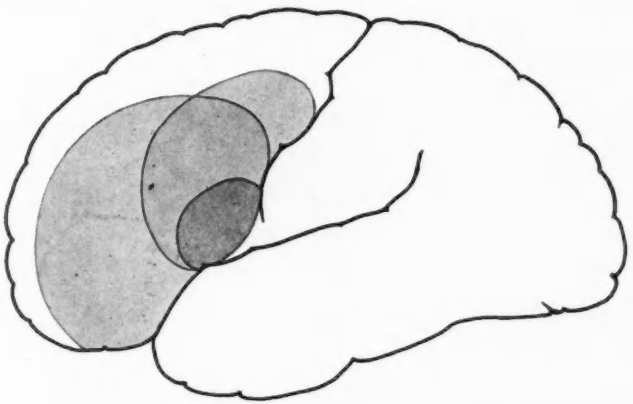

FIG. 9.

In fig. 9 the probable site and extent of these organic lesions have been drawn. It is seen that all are located in the frontal lobe. In the 2 patients with epilepsy the electroencephalographic studies demonstrated an abnor-

mality over the frontal lobe: in 1 of these 2 subjects an occasional spike focus was also observed in the anterior half of the homolateral temporal lobe.

Sub-Group 2.—Parietal. Number of Subjects 8

In all 8 of these subjects the parietal lobe was found to be the site of an organic lesion. In 3, an angioma was demonstrated by arteriography, and in 2 a parasagittal meningioma was removed at operation. In a further 2 subjects gliomata located high in the parietal lobe were found at operation. The last subject had suffered a vascular insult in early life with resulting symptoms referable to a parietal lobe lesion. This was confirmed by the history and by ventriculography. The following particulars are given of 1 of the subjects in whom an angioma was found to be present:

E. S. (Hosp. No. 2408), aged 46 years, had suffered from focal attacks for seventeen years. The attacks commenced with a feeling of deadness in one hand, or with a sensation which she was unable to describe and which affected the left side of her body; either sensation was followed immediately by a loss of consciousness. Examination revealed that she had no defect in her fields of vision. She had a mild left hemiparesis with an equivocal plantar response on that side; there was marked disturbance of sensation involving mainly the left arm and leg; she did not appreciate passive movement in these limbs and two-point discrimination was grossly impaired. On auscultation of the skull a loud systolic bruit was heard loudest over the right parietal region. Arteriography demonstrated a large vascular abnormality situated in the upper part of the parietal lobe and extending forward into the region of the motor cortex.

The site and extent of the lesions found in these 8 subjects, as demonstrated either by arteriographic or by ventriculographic studies were inscribed on an outline drawing of the brain and the result is shown in fig. 10. This makes clear the concentration of the lesions within the

FIG. 10.

parietal lobe. In all but one subject the level of the lesions was high, the exception being in the case of an angioma situated mainly in the lower part of the parietal lobe near to the commencement of the post-central gyrus, at which point an extension of the abnormality occurred, into the deep structures of the anterior half of the temporal lobe. This extension explained the presence of an upper quadrantic hemianopia. In no other subjects was there any field defect present.

Sub-Group 3.—Temporal. Number of Subjects 6

In each of these 6 subjects the clinical findings were indicative of a temporal lobe lesion. In 4 the organic nature of the lesions was evident. The first suffered a gun-shot wound with damage limited to the anterior half of the temporal lobe: the second had a calcified mass in that region displayed by X-ray examination. In the remaining 2, temporal lobe explorations were carried out. In 1 of these the deeper structures, including part of the hippocampus, had been removed and in the other, five years after needling of the anterior half of the lobe, followed by deep X-ray therapy, gliosis of the hippocampal region with discoloration of the white matter in the anterior half of the temporal lobe was demonstrated post

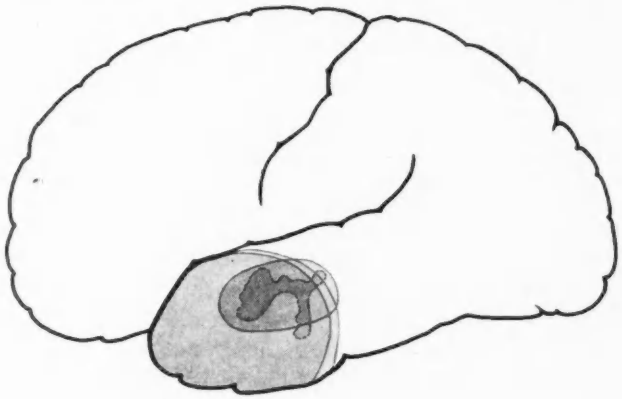

FIG. 11.

mortem. No pathological condition was observed in the posterior half of the superior and middle temporal gyri or in the supramarginal or angular gyri. In the 2 remaining subjects who suffered from epilepsy, the character of the attacks indicated a dysfunction of the temporal lobe. In both these subjects a spike focus was found by electroencephalography to be located in the anterior half of the lobe. The following details concerned 1 of 4 subjects with organic lesions:

W. H. (Hosp. No. 34333), a woman of 27, had suffered from tinnitus since the age of 7. At the onset of an attack she experienced a peculiar sensation in her head. This was followed by a sense of rotation and she felt as if she were in another world. Occasionally she had a sensation in her nose but was unable to recognize it as an odour. Close examination indicated a right upper quadrantic involvement as the only abnormality which could be linked with any disease of the cerebral hemispheres. She also had a myopathic condition. X-rays of the skull revealed a calcified area in the white substance of the anterior half of the left temporal lobe.

The localization and extent of the lesions in the 4 subjects with organic disease is shown in fig. 11. This makes clear that the lesions are confined to the anterior half of the temporal lobe.

Group III.—*Directional Preponderance Present of Caloric Nystagmus without Directional Preponderance of Optokinetic Nystagmus*

A combination of directional preponderance of caloric nystagmus without directional preponderance of optokinetic nystagmus was encountered in 13 subjects. Spontaneous nystagmus was absent. In all of these it was possible to establish with accuracy the site, extent and nature of the supratentorial lesions. The group has proved to be of especial interest since, by careful analysis of the symptoms and signs it has been possible to establish the fact that in all of the subjects a particular zone of the hemisphere was disorganized by disease, a finding which makes explicable upon a focal basis the constant occurrence of directional preponderance of the caloric responses. In 2 of the subjects cerebral angiomata were present, the localization of which could be accurately established by means of arteriography. A further 2 subjects developed temporal lobe abscesses secondary to ear infection. These abscesses had been drained several years prior to our examination. In 2 subjects cerebral tumours had been exposed at operation and accurately located. 2 other subjects had sustained cerebral vascular lesions during early life, and in these the clinical findings, together with the results of air encephalography and electro-encephalography made possible an accurate definition of the site and extent of the lesions. The 5 remaining subjects of this group complained of epileptic attacks. The character of these attacks indicated their origin from foci the location of which could be specified with reasonable accuracy. The clinical findings in 3 typical subjects of this group will be described in some detail.

J. C. (Hosp. No. 7365), aged 21 years, had suffered for as long as she could remember from recurrent severe headaches, which were always located in the left frontal region, and had recently been preceded by visual disturbance in her right field of vision. Sometimes the headaches were followed by an inability to understand the spoken word. More recently in a few attacks she had weakness of her right leg and right arm. Examination revealed that she had a mild nominal aphasia and a

right upper quadrantic hemianopia; there were no indications of a hemiparesis nor of any sensory disturbances, and her reflexes were normal throughout. Palpation of the skull revealed no abnormality, but on auscultation there was a systolic bruit which was most audible in the region of the left mastoid process. X-rays of the skull showed heavy vascular markings of the left middle meningeal artery and arteriography demonstrated a vascular abnormality in the region of the posterior part of the temporal lobe; there was no extension into the parietal lobe.

The symptomatology, physical findings and the arteriogram placed the lesion in the posterior end of the left temporal lobe.

D. S. (Hosp. No 15391), a young lad, had suffered in 1934 from a left otitis media, complicated by a left temporal lobe abscess; the abscess was successfully drained. Since then he had suffered from attacks in which he experienced a sensation in the abdomen and a feeling of dizziness, following which unconsciousness set in. On examination no aphasia was detected, but a right upper quadrantic hemianopia was present. No motor weakness or sensory disturbance was found and the reflexes showed no changes. The electroencephalogram demonstrated a spike focus in the left temporal region.

The history, with the operative findings, indicates that this patient had an organic lesion, the result of an otitic abscess involving the posterior part of the left temporal lobe. It is clear from the clinical findings that no other lobe had been involved.

D. U. (Hosp. No. 6382), aged 17 years, commenced to suffer from attacks at the age of 14. In the attacks he became aware of an indescribable sensation in the abdomen, sometimes associated with a strong element of fear. Observation during an attack showed that his head and eyes turned to the left, while the left corner of the mouth twitched. He had never fallen, and had no recollection of what had occurred in any attack. Sometimes he might undertake automatic movements for several minutes; for instance he might turn round, if an attack came on while walking, and make his way in a direction opposite to that in which he was going. He also experienced bursts of temper, many of which occurred without provocation. Detailed clinical examination revealed no abnormal signs and in particular no hemianopic disturbance was elicited. On several occasions a focus of spikes in the electro-encephalographic record was located in the posterior temporal region.

From the lad's description of the onset of his fits, the nature of the attacks and the E.E.G. findings, it is fair to conclude that he had an abnormality of function located in the posterior part of the temporal lobe.

An anatomical study of the lesions found in the various subjects of this group was made and provided interesting results. Thus, in the 2 subjects with cerebral angiomata the lesion was found to be in the temporal lobe extending into the posterior half. In the 2 subjects with otitic abscesses of the temporal lobe it seems, too, that the posterior half of this lobe must have been involved since the normal spread of a middle-ear infection takes place via the tegmen tympani which underlies this part of the brain. Again, in the 2 subjects with cerebral tumours, both were clearly seen at operation and found to involve the posterior half of the temporal lobe. It has thus

been possible in these 6 subjects to plot the site of the lesions with considerable accuracy. The results are displayed in fig. 12, which makes very

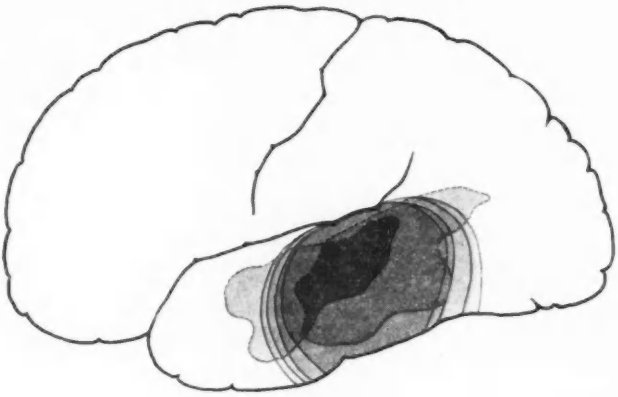

FIG. 12.

clear that an area of overlap exists in the posterior half of the temporal lobe, apparently involving the superior and middle temporal gyri. In the 2 other subjects with occlusive vascular lesions occurring in early childhood, an analysis of their symptoms and signs, together with air-encephalographic findings, also show that the posterior part of the temporal lobe was chiefly involved. Finally, in all the 6 subjects with epilepsy their attacks were of a type suggestive of temporal lobe pathology. In 2 of these subjects this was supported by the electro-encephalographic findings, while in another air encephalography showed a dilated temporal horn in the hemisphere indicated as abnormal by the clinical evidence.

Throughout the group of 13 subjects the severity of the directional preponderance of the caloric response bore no relationship to the pathology or extent of the cerebral lesions. A further point of importance is concerned with the occurrence of defects in the visual fields. In 7 of the subjects the visual fields were normal. Of the remaining 6, 5 had an upper quadrantic defect, and the sixth had a hemianopia with sparing of the macula. It is thus shown once more that the occurrence or otherwise of a directional preponderance of caloric responses is quite unrelated to the existance of defects in the visual fields.

It will, therefore, be seen that the evidence presented makes it reasonable to identify the posterior half of the temporal lobe as the zone of the hemisphere, the destruction of which is responsible for the directional preponderance of the caloric responses.

GROUP IV.—*Directional Preponderance Present of Optokinetic Nystagmus. Directional Preponderance of Caloric Nystagmus, Absent or Slight*

This combination of directional preponderance of optokinetic nystagmus with absence or relatively slight preponderance of caloric nystagmus was encountered in 3 subjects. In all 3 it was possible to establish with accuracy the site, extent and nature of their supratentorial lesions.

In the first 2 subjects lesions of the occipital lobe were present and in the third a lesion of the supramarginal and angular gyri.

A. *Occipital lobe lesions.*—Details of the 2 subjects with occipital lobe lesions are appended:

S. D. (Hosp. No. 34151), a child aged 6 years, was admitted with severe headaches and head retraction. The cerebrospinal fluid was blood-stained. Arteriography revealed an angioma in the infero-mesial aspect of the left occipital lobe. At operation the angioma was found in the region of the left calcarine fissure; it extended down to the trigone which was opened when the angioma was excised. Three months later a complete right-sided hemianopia with macular splitting was found; no motor, reflex or sensory disturbances were elicited. At otological examination the caloric responses were normal, but there was a slight but definite directional preponderance of optokinetic nystagmus to the left.

B. T. (Hosp. No. 28795), an adult of 27 years, gave a history of repeated severe headaches. On admission lumbar puncture carried out during such a headache revealed a blood-stained fluid. Perimetry showed a complete loss of vision at the periphery of the lower left quadrant, with an incomplete loss in the remainder of the left half of the fields of both eyes. Arteriography showed an angioma lying anteriorly in the region of the right calcarine fissure. No disturbance of caloric responses was elicited, but there was a slight but definite directional preponderance of optokinetic nystagmus to the right. At operation an angioma presented anteriorly in the calcarine fissure; this was excised and in the course of the operation the trigone was opened. Examination of the tissue removed showed that its boundaries extended up to, but did not exceed, the limits of the occipital lobe. On examination fourteen days later a complete left hemianopia with macular splitting was found. No motor or sensory disturbances could be detected, and the reflexes were normal. Otological examination revealed no preponderance of caloric nystagmus, but the preponderance of optokinetic nystagmus to the right was still present.

A study of the caloric and optokinetic responses in these 2 patients indicates firstly that lesions causing a hemianopia and involving both lips of the calcarine fissure, did not bring about any derangement of the caloric response; secondly, that they did bring about some directional preponderance of the optokinetic responses to the side of the lesion. It is necessary to stress that the amount of this preponderance was in both cases inconsiderable and in the second case repeated observations were needed to establish its presence. It would, therefore, appear that lesions of the occipital lobe, even when they involve the entire visual cortex with resultant complete hemianopia with macular splitting, bring about no

more than a slight directional preponderance of the optokinetic responses. This conclusion accords well with the results of our observations upon another subject not included in this group in whom an angioma was found involving part only of the calcarine fissure. Particulars of this subject are appended:

A. C. (Hosp. No. 46974), a child of 6½ years, developed severe headaches with neck rigidity. During one such headache the cerebrospinal fluid was blood-stained. Perimetry revealed no abnormality. Arteriography demonstrated an angioma in the region of the left parieto-occipital sulcus. Owing to the presence of impacted wax in the ears caloric responses were not investigated; there was no disturbance of optokinetic responses. At operation an angioma was excised from the region of the parieto-occipital sulcus; it extended into the anterior part of the superior lip of the calcarine fissure. The ventricle was not entered, nor was the lower lip of the calcarine fissure involved. A month after operation the only visual defect was a small indentation at the periphery of the right lower fields near the mid-line. The rest of the right field was normal. No motor, reflex or sensory disturbances could be elicited and the reflexes were normal. At otological examination both caloric and optokinetic nystagmus were normal.

The site and extent of the lesions, as demonstrated by arteriography in the occipital lobes of these 3 subjects (S. D., B. T. and A. C.) is illustrated on an outline drawing in fig. 13.

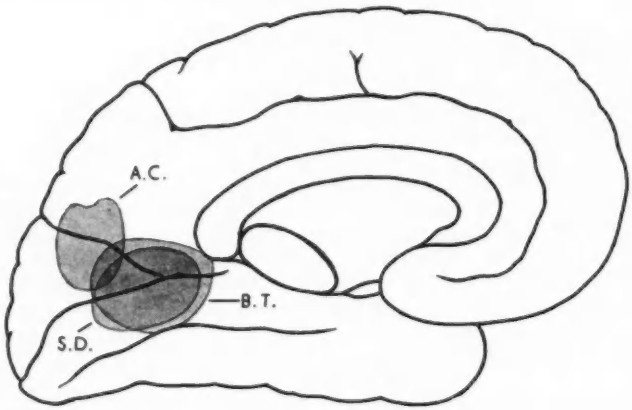

FIG. 13.

B. *Lesions of the supramarginal and angular gyri.*—In this subject well-marked directional preponderance was observed of the optokinetic responses accompanied by a comparatively slight directional preponderance of the caloric responses. The clinical and post-mortem findings provided proof of the existence of an organic lesion involving the temporo-parietal cortex in the region of the supramarginal and angular gyri.

W. T. (Hosp. No. 43289), a man of 50 years, had been admitted because of headaches and exhibited a left homonymous hemianopia, a failure of the discriminatory function in the left side of the body and a left extensor plantar response. At post-mortem he was found to have a normal superior temporal gyrus, gross flattening of the supramarginal gyrus and tumour tissue immediately beneath the angular gyrus of the right hemisphere. Three weeks before death there was an extreme degree of directional preponderance to the right of the optokinetic responses with a slight but definite caloric preponderance to the right.

The positive findings of a severe directional preponderance of optokinetic nystagmus in this case (W. T.) taken in conjunction with the comparatively minor degree of the preponderance observed in our subjects with occipital lobe lesions, certainly points to the conclusion that the supramarginal and angular gyri play a much more important rôle in the directional control of the optokinetic responses than do the occipital lobes.

This conclusion has been greatly strengthened by a series of further observations upon 3 additional subjects in which a selective increase of optokinetic nystagmus has resulted from an operation involving these 2 gyri. Details of these subjects are appended:

I. P. (Hosp. No. 13769), a young woman, aged 25, had suffered since the age of 18 months from a right hemiplegia, fits and severe behaviour disorder. Examination had shown that she had a right-sided hemianopia, right-sided sensory disturbances and right hemiparesis. Air encephalography revealed diffuse enlargement of the left ventricle. Otological examination on several occasions over a period of many months showed preponderance of both caloric and optokinetic nystagmus to the left. The directional preponderance of the optokinetic nystagmus was always slight compared to the directional preponderance of the caloric nystagmus. Electrocorticography revealed a spike focus in the region of the supramarginal and angular gyri on the left side, and these gyri were excised. On examination five months later there was a well-marked directional preponderance of both optokinetic and caloric nystagmus.

Thus the removal of the 2 gyri resulted in selective increase of the optokinetic directional preponderance; no further change followed hemispherectomy.

R. J. (Hosp. No. 39401), a boy aged 11 years, suffered from fits since the age of 2½ years. He was mentally backward and found to have a left hemianopia. Air encephalography revealed distension of the right ventricle in the region of the trigone. At craniotomy a small piece of cortex was removed from the posterior half of the right temporal lobe. Some months following this excision he was found to have a marked preponderance to the right of the caloric responses with a comparatively slight directional preponderance of the optokinetic responses. At a further operation more of the lateral aspect of the temporal lobe was removed, for which the incision passed through the supramarginal and angular gyri. At an otological examination carried out one month afterwards, and repeated several months later, a severe preponderance to the right was found of both the optokinetic and caloric responses.

It is clear that at this second operation the supramarginal and angular gyri were removed as well as the remaining portion of the posterior third of the temporal lobe, and thus we are led to conclude that its effect was to

bring about the selective increase of the directional preponderance of the optokinetic responses to match that of the caloric responses.

B. T. (Hosp. No. 12534), a lad aged 15, suffered from fits, the character of which indicated disturbance in the right parietal region. Examination revealed a left lower quadrantic homonymous hemianopia with some defect in two-point discrimination in the left leg. Air encephalography revealed a large cyst in the right parietal lobe extending to the mid-line and down towards the Sylvian fissure. There was a very well-marked preponderance of the caloric responses to the right with a slight degree of preponderance of the optokinetic responses. At operation the cyst was found to present on the lateral surface of the parietal lobe, and an incision was made into the brain at its inferior and anterior edge in the region of the supramarginal gyrus. Otological examination after the operation showed a marked increase of the optokinetic preponderance.

Thus a marked accentuation of directional preponderance of the optokinetic responses was observed to follow an incision into the supramarginal gyrus.

Our findings in these 3 subjects (I. P., R. J. and B. T.) thus provide additional evidence of the essential part played by the supramarginal and angular gyri in the directional control of the optokinetic responses.

The site and extent of the lesions involving the supramarginal and angular gyri in these three subjects and also in the patient W. T. are illustrated on an outline drawing in fig. 14.

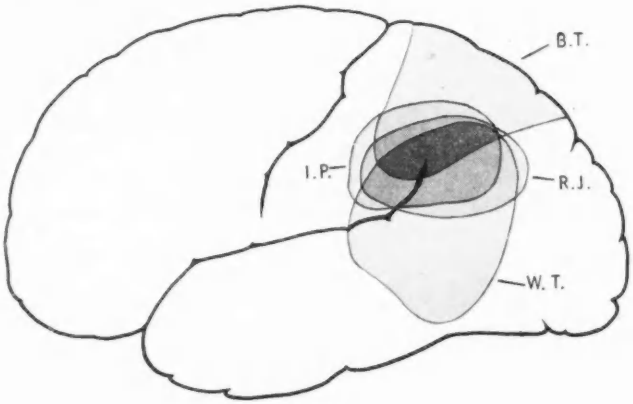

FIG. 14.

RESULTS AND DISCUSSION

The clinical findings given in the preceding section of this communication may be summarized as follows:

(1) Directional preponderance (D.P.) of either caloric nystagmus (C.N.) or of optokinetic nystagmus (O.N.) was absent in all subjects with lesions

limited to the frontal lobe, the upper half of the parietal lobe or the anterior half of the temporal lobe.

(2) D.P. of C.N. to the side of the cerebral lesion without D.P. of O.N. was a constant finding in subjects with lesions limited to the posterior halves of the temporal lobes.

(3) D.P. of both C.N. and O.N. was a constant finding in subjects with lesions involving not only the posterior halves of the temporal lobes, but also the regions of the supramarginal and angular gyri upon the same side. Furthermore, surgical interference in the region of the supramarginal and angular gyri in several of those subjects resulted in a selective increase of D.P. of O.N.

Upon the basis of these findings we have concluded that the directional control of caloric and optokinetic nystagmus is normally exercised through independent nervous mechanisms situated respectively in the posterior parts of the temporal lobes and in the supramarginal and angular gyri.

In the majority of earlier investigations, some reference is made to the part played by the frontal lobes in the directional control of nystagmus. Thus, Stenvers believes that the frontal lobe is an essential station in the optomotor pathway, and this possibility is not excluded by Fox and Holmes. Other authors, however, including Cords, make it clear that at any rate in some of their cases disease of the frontal lobes was present without any abnormality of induced nystagmus. Included among our own subjects are many instances of frontal lobe lesions without any evidence of D.P. of either C.N. or O.N. and upon these findings we think it justifiable to conclude that the frontal lobes play a negligible part in the directional control of either Optokinetic Nystagmus (O.N.) or of Caloric Nystagmus (C.N.).

Our conclusions as to the influence of certain portions of the parietal and temporal lobes have involved a number of uncertainties; perhaps inevitable in view of the complexity of the clinical data. Thus Wycis and Spiegel (1953) have recently expressed the view based on their experimental findings in cats and dogs that preponderance of vestibular nystagmus, caloric or rotational, is better considered as a secondary effect of a lesion of the optic radiation and not of any independent mechanism in the temporal lobe. It does not, however, seem possible to explain our findings in this way since in a number of our subjects [Group IV (S. D., B. T. and A. C.) Group II (W. H. and 1 other)] obvious clinical evidence of lesions of the optic radiation in the form of gross visual field defects has been unaccompanied by any D.P. of C.N.

We have considered also a further possibility which would make unnecessary the attribution to a temporal lobe lesion of D.P. of C.N., namely

that it arises as a secondary result of a lesion of the cerebral optokinetic mechanism. This possibility also appears to be clearly contradicted by our findings. Thus, if D.P. of C.N. arose as a secondary effect of a lesion of the optokinetic mechanism, then we could hardly expect its occurrence without some demonstrable abnormality of O.N. In point of fact, we have frequently found it in conjunction with normal optokinetic responses. It could, perhaps, be argued that the caloric mechanism is, in some way, not easy to explain, extremely susceptible to derangement and that for this reason D.P. of C.N. might be brought about by a lesion of the optokinetic mechanism which did not cause any demonstrable derangement of O.N. The acceptance of an explanation of this kind would compel the expectation that demonstrable defects of O.N. must always be accompanied by relatively severe defects of C.N. This, however, has not been our experience and our figures from Group 4 show quite clearly that in the presence of well-marked preponderance of O.N., preponderance of C.N. may be slight (W. T.) and may sometimes be completely absent (S. D. and B. T.)

Assuming therefore that it is possible to accept the directional control of C.N. and O.N. through independent nervous mechanisms in the parietal and temporal lobes, it remains to consider and compare the manner in which they exert their effects.

(1) *The vestibular mechanism.*—The organization of the brain-stem mechanism which subserves vestibular nystagmus was clearly established by the experimental work of de Kleyn (1939) who showed that vestibular nystagmus could be induced in the absence of the cerebral hemispheres. The neural elements necessary for induced labyrinthine nystagmus were given by de Kleyn as follows: Peripheral labyrinth and vestibular nerve, vestibular nuclear areas in the brain-stem, abducens nuclei, abducens nerves and external rectus muscles.

Fitzgerald and Hallpike described the influence of the temporal lobe upon induced vestibular nystagmus as a modifying effect, exerted upon the reflex responses of the lower vestibular centres, and of a nature in general accord with what is known of cortical influences upon other kinds of reflex activity.

(2) *The optokinetic mechanism.*—It has seemed to us reasonable to expect that this would exhibit the same functional pattern which we have attributed to the vestibular mechanism. Thus the lower centres, paired as in the case of the vestibular nuclei, are found in the superior colliculi, from which further pathways pass to the eye muscle nuclei. Superimposed upon each of these centres, left and right, we have the left and right cerebral centres in the supramarginal and angular gyri. These centres, though not essential for the optokinetic responses, do, nevertheless, modify

them, each in a particular direction. In this way a unilateral cerebral lesion, involving one of these centres, will cause D.P. of O.N.

This conception does not, however, seem to accord with the views of Rademaker and ter Braak (1948) who prefer a much more clear-cut separation of the cortical and subcortical mechanisms. In particular they attribute their cerebral type of O.N. to a mechanism dependent upon macular fixation and subserved by pathways and centres in the brain-stem which they suggest may be independent of those involved in their subcortical type of O.N.

Certain observations of our own are difficult to explain upon the basis of these views. The observations were carried out upon a number of our subjects with unilateral hemispherical lesions. When tested with our rotating drum, a small visual stimulus, all exhibited D.P. of O.N. to the affected side. The D.P. of O.N. obtained under these circumstances would, according to the hypothesis of Rademaker and ter Braak, be due to a defect of the mechanism of cerebral O.N. The same subjects were then tested within a large revolving cylinder, presenting a full field display of moving lines. Now, according to the hypothesis of Rademaker and ter Braak the optokinetic responses thus obtained would be derived from the independent subcortical reflex pathways. Assuming the integrity of these pathways, the nystagmus would not be influenced by a unilateral cortical lesion, and would therefore be equal to both sides. In point of fact we have constantly found that in such cases a D.P. of O.N. obtained with the small visual stimulus is also present, although in a less obvious form, within the large revolving cylinder. It is, of course, possible to interpret this finding upon the basis of Rademaker's and ter Braak's hypothesis by attributing it to some concomitant lesion of the lower reflex pathways. We have not been able to exclude this possibility but consider it remote, and our conclusions based, we think, upon the balance of evidence may be stated as follows:

The optokinetic responses to the left and right are subserved primarily by anatomically separate reflex pathways within the brain-stem. Each of these pathways is under the modifying influence of a centre in the supramarginal and angular gyri of a particular cerebral hemisphere. Thus, the centres of the right hemispheres facilitate O.N. to the left and inhibit it to the right, while the opposite effects are exerted by the centres of the left hemisphere. This arrangement finds a parallel in the organization which we have postulated for the neural mechanism of vestibular nystagmus. This, as our clinical data have clearly indicated, is primarily dependent upon the lower vestibular pathways, subject to the same directional influences of centres in the posterior parts of the temporal lobes.

Acknowledgments

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BALINT'S SYNDROME (PSYCHIC PARALYSIS OF VISUAL FIXATION) AND ITS MINOR FORMS

BY

H. HÉCAEN AND J. DE AJURIAGUERRA

(From the Neurosurgical Service, Hôpital Ste Anne, Paris)

IN 1909 Balint described a syndrome which he called "psychic paralysis of visual fixation," in which the disturbance of fixation occurred in association with an "optic ataxia" and a disturbance of visual attention. This syndrome, as described by Balint, has appeared in the literature very rarely. Only one observation of Gordon Holmes (1918) and one observation published by us (1950) seem to accord with the original description of the German author.

The patient described by Balint showed three kinds of disturbances:

(1) Psychic paralysis of visual fixation is apparent in the patient's inability to look towards a point which is in his peripheral visual field. The author justifies his term of "psychic paralysis" by the fact that, in certain circumstances, when higher psychological functions are not involved, ocular motility is found to be normal.

(2) "Optic ataxia" can be elicited by the whole range of tests which are designed to examine the patient's ability to execute co-ordinated voluntary movements in response to visual stimuli. The author compared the failure of visual control in this case with the impaired proprioceptive control of the tabetic. In fact, the latter partly corrects his ataxia when he is permitted on sight instead of on his defective proprioception. Balint's patient, on the other hand, executed certain movements correctly under proprioceptive control despite his inability to control movements visually.

(3) Disturbance of attention: The patient's attention is normal for all non-visual stimuli; for visual stimuli, however, there is general impairment of attention. Consequently only the most prominent stimuli (namely those at the macula) actually reach consciousness. The others (at the periphery) are not seen by the patient, although his "absolute" visual field is normal and the peripheral visual apparatus is capable of normal function. Moreover, this disturbance was more noticeable for the left side than for

the right, the patient's attention being always directed spontaneously towards the right.

In Holmes' case of a patient with a traumatic bilateral lesion (shrapnel wound) we can schematically identify the three classes of phenomenon distinguished by Balint.

(*a*) The patient could neither move his eyes to command nor follow the motion of an object. Reflex motility was nevertheless intact. As soon as the object left the central field of vision there was great difficulty in locating it. There was complete inability to estimate the distance between two objects standing in different relationships to himself. The patient said, "I can only see one at a time." In counting objects in line, he counted only one or two, making no effort to look further along the line. There was great difficulty in fixing upon the objects which were not in central vision (the eyes wandered until, by chance, the objects fell into central vision).

(*b*) When the patient wanted to grasp an object he extended his hand in the wrong direction and only succeeded after repeated groping.

(*c*) There was visual inattention for obstacles and he frequently bumped into things. He did not turn his eyes promptly towards a light flashed suddenly from the side. He could not find his way although he could see where he should be going and describe the route.

In addition to these disturbances, the patient showed some language difficulties, agraphia and ideomotor apraxia. But, with the exception of the disabilities described above, stereoscopic vision, gnosis and visual memory were preserved.

Case 1.— The patient we described with Rouques, David and Dell (1950) showed, on examination, a number of disturbances of symbolic functions.

(1) Language disturbances of the Wernicke type with agraphia and alexia.

(2) Apraxic disorders: global ideomotor and constructional apraxia and apraxia for dressing.

(3) Agnosic disturbances: there were no obvious disturbances of body perception but the difficulties of examination prevented any definite conclusion. Recognition of objects was good but there were pronounced difficulties in matching and indicating colours.

We were able to distinguish the three kinds of disturbance which characterize the syndrome described by Balint and these may now be briefly described:

(1) Psychic paralysis of visual fixation. There was inability to make voluntary eye movements and considerable inattention for everything outside the area of central vision. In lighting a cigarette, when the flame was offered to him an inch or two away from the tip of a cigarette held between his lips, he was unable to see the flame because his eyes were fixed on the cigarette. There was also absence of visual pursuit movements.

(2) Optic ataxia was shown by marked errors when he attempted to grasp an object at which he was looking. In Balint's case, this disorder was lateralized: it was much clearer in the case of the right hand than the left. In our patient the reverse obtained, since errors were more marked in the case of the left hand.

(3) Disorders of visual attention: the patient's spontaneous attention for any visual stimulus was markedly decreased and was concentrated on events occurring precisely at the fixation point. In short, there was a kind of concentric narrowing of the field of attention. Like Balint's patient, he was perfectly able to encompass in a single fixation a relatively extensive field, provided only a single object was involved. For instance, he easily recognized people confronting him although, at the same distance, he was unable to see two small objects simultaneously, such as two pencils placed two inches apart, or the tip of his cigarette and the flame of a match.

Another example demonstrated the same phenomenon: the patient walked along the corridor as though blind, with his arms stretched out in front of him. He might hit his forehead violently against a closed glass door, which he attempted to walk through. When questioned he explained with gestures that he did not see it. However, when the stairs at the other end of the corridor, 18 yards away, were pointed out to him, he saw them quite well. We may suppose that, in this case, the glass door was not seen because it was too near the patient and consequently did not constitute a coherent whole which could be registered in his visual field; the stairs on the other hand, seen in a single glance, retained their unity and were thus promptly identified.

The most striking of these three observations is the inability to shift from a point of fixation. But, as an isolated symptom, this "locking" of fixation is a comparatively common observation. It occurs in the literature fairly often, either taking the form of reading difficulties or simply appearing as what Kleist calls "weakness of peripheral fixation" (that is to say difficulty in directing the gaze towards a point in the peripheral field when already fixing upon a given point). Or, again, it may be apparent in counting-difficulties as described by Best—inability to count a series of identical objects. It is this "locking" of fixation, which is a secondary symptom and not itself a primary disturbance, that most authors have called Balint's psychic paralysis of fixation (Lhermitte and Mouzon), 1941; Mollaret, Bernard and Pluvinage, 1941; David and Hécaen, 1943; Guillain, Iereboullet and Brisset, 1947.

On the other hand, when Holmes described this symptom he called it after Gowers "spasmodic fixation" and rightly compared it to the spasmodic paralysis of a limb which is characterized on the one hand by increased tone, tending to immobilize the limb in a certain position with resistance to passive movement, and on the other hand by a loss of strength and reduction of voluntary movement.

But cases can occur in which the symptomatology is much closer to the true cases of Balint's syndrome without necessarily showing the three essential features, or else showing them in a transitory and fragmentary fashion.

It seems to us important to pursue observations of this kind and then to define the essential symptoms which justify the claim that a case is a minor form of this syndrome and not merely spasmodic fixation. This is important from the semiological and the practical point of view, since psychic

paralysis suggests, even in its minor forms, a bilateral lesion. This occurred in Hoff and Pötzl's case (1935) where the patient saw only parts of the objects and guessed at the shape on the basis of these parts. She could read only words which were seen in a single fixation. When asked to look to the left she only turned her head. On the other hand she could follow an object moving slowly to the left. An element of unilateral spatial agnosia seemed indisputable in this case. Post-mortem examination revealed a double lesion: extensive softening of the right parieto-occipital convexity and small areas of softening in the region of the left posterior cerebral artery.

The following are three cases which we have seen of which two have been anatomically verified and may be classified as minor forms of Balint's syndrome.

Case 2.—Paulette C., aged 28, right handed, seen at l'hopital Henri Rousselle in June 1949, complaining of reading difficulties following a series of illnesses incurred in January 1946 during her pregnancy.

No relevant family history.

Pregnancy in July 1945. This progressed normally without fatigue, but in January 1946 two typical convulsive seizures occurred. There was albuminuria. She was put on a diet and the pregnancy proceeded normally until January 27, when there was violent eclampsia. Delivery occurred next day after artificial dilatation and the use of forceps. The patient remained in a comatose state for three days and, after this episode, became excited and confused, with dimming of vision. For several days she continued to have subintrant seizures. Pulmonary congestion and also bilateral phlebitis appeared during this period. The amaurosis persisted for three months. During this period the patient could neither dress herself nor attend to her hair; she could not eat unaided and was clumsy on the left side. When she began to see again she nevertheless bumped into things; when she wished to grasp an object she overreached or reached to the side of it. At this stage she was completely alexic and agraphic but it should be noted that at no time was there any obvious aphasia.

After nine months she began to read but had difficulties in following the lines and mixed up the order of the different letters and words. Her husband mentioned that, at this time, her eyes moved but still failed to fixate the letters. In writing she was hindered by the presence of lines on the paper because she could not follow them. She still had difficulty in combing her hair and in dressing and confused her left and right sides.

There was continuous improvement, particularly with respect to dressing, washing, etc., but the dyslexic and dysgraphic difficulties persisted. The husband reported some curious observations: she always walked in the middle of the road if left alone, and, in a vehicle, attempted to sit on a seat the wrong way round.

A typist by occupation, she remained unable to work at her machine.

Examination during June 1949.—General neurological examination was negative especially with respect to motor and sensory functions.

Ophthalmological examination (Dr. Magis): V.A. 6/6; fundus normal.

The visual fields showed a defect encroaching deeply on the mid-line from both extremes of the vertical dimension, but sparing foveal vision (fig. 1).

Mental state.—She appeared very childish with some mannerisms; no confusional features and no dementia but she tired very easily.

Language.—There was dyslexia and dysgraphia. Reading was difficult except for

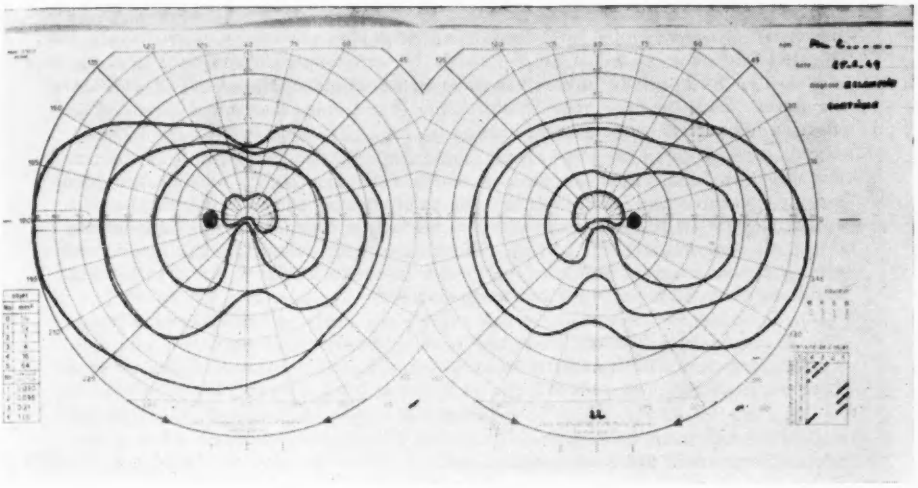

FIG. 1.

isolated letters; she occasionally managed to read words slowly if she followed them with her finger. Even then, she could only read intermittently and jerkily. There was complete failure when she had to move down from one line to another. She was unable to read on André-Thomas', Roux's and Goldstein's tests.

Writing was fairly accurate, especially to dictation; copying was still difficult. She could not keep to a straight line.

Calculation.—Individual digits were recognized but she could not read a number consisting of several digits. She could write individual digits well but put them in the wrong order and this made any arithmetical calculation impossible.

Praxis.—There was no ideational or ideomotor apraxia but she was unable to copy postures adopted by the examiner.

Constructional praxis.—There was complete inability to draw or to assemble the simplest matchstick pattern to command.

There were similar difficulties in copying. There was complete failure on Bender's test, on copying or reconstructing the "manikin," and on copying matchstick patterns. There was complete failure on even the simplest of the Koh's block designs, even with an enlarged model.

Body perception.—Good left-right discrimination on herself and on the examiner but some difficulty with Head's test, especially when the hands were crossed. We elicited some difficulty in naming the fingers as well as in moving them singly to command. Moreover, she confused the different fingers of the examiner's hand.

Visual gnosis.—Good recognition of objects and of simple and complex pictures. It is noteworthy that recognition was assisted if she could underline certain parts of a picture with her finger. She was capable of recognizing a certain number of uncompleted pictures. Each picture in a picture story sequence was perceived but she could not grasp the point of the story. Colours were adequately recognized (Ishihara test).

There was loss of stereoscopic vision and all objects were seen in the same plane. The patient was well orientated with respect to the hospital and even learned her way about Paris quickly.

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Elements of Balint's syndrome.—Although ocular movements to command and automatic movements were well executed, visual pursuit movements were disturbed. She could follow a moving object only with jerky movements and only if it moved very slowly. Except under these conditions she would claim she could no longer see the object. Once she fixed upon an object, her gaze became locked and it needed an effort on her part to change her fixation.

When an object in front of her was fixed in this way the patient did not react to the slow introduction into her field of vision of another object, moving from the periphery to the centre. This was the case irrespective of whether the second object was moving to the left or to the right and the only exception was when the second object was almost touching the first. We have already mentioned the inability to read sentences except with jerky movements and, similarly, we showed that she could not move down from one line to another.

On Poppelreuter's test she perceived objects separately and sometimes only one part of an object, and so she described isolated fragments of the whole assembly. Similar observations were made in the case of uncompleted pictures. When asked to leave the room she turned towards the door but was unable to find the handle.

Optic ataxia.—When trying to grasp an object presented to her from different angles, she moved her hand towards the object but stopped well short of it and then cautiously advanced her hand until she touched the object. She could not grasp the object with a single movement; the movements were slow and disjointed.

Although visual acuity was normal and the peripheral field showed no disturbances, she bumped into things on the right side when walking.

A sharp unexpected noise, whether on the right or the left, produced a blinking reaction but no oculogyric movement.

The E.E.G. showed slow diffuse abnormalities, predominantly in the left hemisphere.

Encephalography revealed diffuse cortical atrophy.

Summary.—A woman, aged 28, during eclampsia, developed a confusional state of short duration and an amaurotic episode lasting three months. Apraxia for dressing, alexia and agraphia lasted for nine months.

On examination three years later we found dyslexic difficulties without any other language disturbance, a "quasi-spatial" acalculia, a very marked constructional apraxia, some finger agnosia, no simultaneous agnosia or agnosia for colours and loss of stereoscopic vision. In addition, there were oculomotor disturbances which gave rise to certain disturbances of reading and of visual recognition, together with slight "optic ataxia" and visual inattention.

The visual field showed a defect encroaching deeply on the mid-line from both extremes of the vertical meridian, but sparing foveal vision. This would be typical of a bilateral occipital lesion (Dubois-Poulsen and Magis).

Case 3.—Elisabeth A., aged 59, probably ambidextrous (sews, writes with the right hand, uses the left hand for some more powerful movements) was referred to us on September 13, 1950, by Dr. Hedouin with suspected cerebral tumour.

History of illness.—Her husband had noticed that for several months her memory had given trouble. In August 1950 there was a confusional episode with aphasia. She remained disoriented for time, being unable even to remember her age. Although

she knew where she was she would nevertheless get lost in her own house. At about the same date abnormal movements of the left hand appeared. She had frontal headache without nausea and episodic blurring of vision.

Family history negative.

Examination.—Increased extensor tone on the left side, with some sensory loss involving the left leg. In the left arm astereognosis was present but position sense was intact.

The left hand was held in a fixed posture, the index hyperextended and the thumb adducted with flexion of the first phalanx. Before long, progressive flexion of the other fingers was observed. If her attention was drawn to her hand she moved it, changing the posture, only to assume it again when attention shifted from her hand. In movement, the left hand sometimes reached out to grasp something, pronated with palm upwards.

General intellectual deterioration was present with marked disturbances of attention and emotional lability. She had comparatively well preserved insight into her illness; despite her demented appearance she was able to understand certain references to her health and to appreciate some jokes.

Language was only slightly impaired. The patient showed no dysarthria, could name objects she was shown, could carry out simple and moderately complicated instructions but failed to understand really complex commands. It was not possible to decide whether this should be attributed to language difficulties or to intellectual defect. Reading was accurate. She was able to write spontaneously and to dictation but was unable to keep to a straight line and tended to duplicate the down strokes in letters such as m, n . . .

Praxis.—Ideational praxis was normal. Ideomotor dyspraxia of the left upper limb was present. For example, the finger-nose test might be well executed with the right hand but would be performed uncertainly with the left hand, the fingers being flexed instead of extended. A military salute could be performed accurately with the right hand but spatial disorganization was apparent when the corresponding movement was attempted with the left hand, which was placed flat against the head.

She was also unable to imitate non-directional movements demonstrated by the examiner (holding up 8 fingers, imitating a butterfly with the hands). Each hand was correctly placed but she could not place them together.

Apraxia for dressing.—Disabilities, which were often compensated for by the patient, were disclosed by tests of dressing. At first she could not put on her jacket, wearing it back to front but, on noticing the error, managed to adjust it normally. She tried to tie her head scarf with one end only. In tying the sash of her dressing gown she passed it through one of the loops and tied it around this loop without noticing that she had not passed it around her waist. Then she suddenly exclaimed that she had not tied the sash around herself, untied it and adjusted it correctly. In other acts of dressing faltering hesitations were noticed which were followed by sudden successes.

When the test was complicated by presenting her jacket to her in an unusual position, after an abortive attempt to place her right arm through the sleeve, she held the jacket up before her eyes, tried to put her left arm through the wrong sleeve and so failed a second time.

Constructional apraxia.—Apart from a few simple shapes, such as a square and a triangle, which she could draw or copy roughly, she was unable to draw any shapes spontaneously or copy them from a model. She often drew simple, poorly formed outlines and a certain amount of "closing in" was noticeable in her attempt at copying. When asked to draw an embroidery design of her own invention (previously she was an excellent embroidress) she mentioned violets and drew a few vague petals. In reconstructing a rectangle with pieces of cardboard (model provided) she failed

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completely. Failure occurred even when she was shown how the pieces were placed together.

Calculation.—She was able to write digits well and she could sometimes list the terms of an addition correctly but often she would write the digits too far apart and then try to correct her error by writing them again, but the task remained uncompleted. She was never able to complete the calculation. In reading numbers consisting of several digits, she neglected those farthest to the left. For example, for 2365 she read three and sixty-five. Even when prompted she could not manage to read the number as a whole.

Counting gave rise to two kinds of failure. In the case of scattered objects she only saw the central group and made no attempt to count them.

Unilateral spatial agnosia.—We had already seen from the preceding tests that the patient neglected numbers or objects situated to her left. This neglect of the left side was also observed in reading. When required to read a phrase disposed as follows:

La Semaine
des Hopitaux

she read: Semaine Hopitaux.

When she was roughly examined for hemianopia, using the finger as a test object (the mental state precluded any other method of testing the visual field at this stage), there did not appear to be a genuine field defect provided she was told at the outset that the finger might appear from either side. On the other hand, an object carefully introduced into the visual field without warning was not noticed until it reached the mid-line. However, if, when her fixation was steadily maintained in the mid-line, a flower was presented in her left half-field and she was asked: "Can you see anything to your left?" she would reply, "A flower" and would even say its colour. Neglect of the left side was also apparent if the examiner walked around her bed. Although her eyes followed him to the right, she did not, however, turn her eyes to the left except in response to an auditory stimulus such as a whistle or snapping of the fingers.

Visual gnosis.—Objects, pictures, symbolic shapes and colours were well recognized.

She was unable to tell the time, but her errors were not systematic except for some which appeared to reflect unilateral spatial agnosia, nor could she adjust the hands of a clock to an orally specified time.

Body perception.—Left-right disorientation with respect to the examiner and to objects in the environment were noticed but she had no such difficulties with respect to her own body. Thus she was unable to recognize designs which had similar vertical components but whose upper and lower transverse components had different orientations. The same applied to letters which differed only with respect to their orientation (d and b, p and q). There was no finger agnosia, but there was neglect of the left side. Whilst her clothes were properly arranged on the right side, they were nevertheless disarrayed on the left, except when the patient paid special attention to this side. Moreover, the left side of the body remained remarkably immobile although movement was normal on the right. This immobility sometimes bordered on catalepsy.

If, after her left hand had been placed in a position away from her trunk, she was asked to touch it with her right hand, she had first to move the left hand and then grope for it with her right hand before succeeding. In the same test, if the examiner interposed his own hand she would grasp this strange hand and say, "I don't know if this is my hand." Next she would move her left hand vigorously and say, "Here is my hand" and then reject the examiner's hand and complete the required task correctly. On the right side such tasks were performed immediately and accurately.

Spatial orientation.—The patient, who had previously got lost in her own house, was unable to describe a familiar route. Left to her own devices in the hospital she could find her ward only after many errors, some of which could be attributed to a tendency always to turn to the right. Also there seemed to be great difficulty in recognizing places. She had to examine each bed minutely before recognizing her own. When recognition occurred it was with sudden insight.

Topographical knowledge of a general nature was comparatively well preserved. The patient recognized an outline map of France and could indicate the position of the Channel, Cherbourg (her home town) but could not point to the position of Paris, despite attempts to locate it in relation to Rouen which she could place fairly precisely.

Elements of Balint's syndrome.—Apart from the left spatial agnosia, a particular effect was observed in the left half-field. When two objects were simultaneously introduced into this half-field she never perceived both at the same time, the opposite of what was observed in the right half-field. However, if she happened to glance spontaneously towards the left when she was not being asked to fix, she perceived both of the two objects.

The test was made easier by the fact that, when she had been induced to fix upon the examiner's nose, fixation became, as it were, locked to this point, despite the fact that, at first, fixation was difficult to obtain; for example even when the examiner's face was quite close to hers she would say, "Wait until I can see where your nose is."

In the case of flowers, objects were always well perceived in isolation and were even adequately recognized in the left half-field, but if asked to indicate the position of a flower she would point with her finger to a position immediately in front of her, although the flower might be well over to her left. When asked to take hold of the flower, she would touch the face of the examiner in front of her. This was the case whichever hand was used. It is noteworthy that the same effect was found in the case of an object in her right half-field.

When not fixing upon the examiner she was quite easily able to take hold of a flower in her left half-field with her right hand, but she always reached directly in front of her when required to grasp the flower with her left hand.

When three flowers were placed before her in a row, she was able to say how many there were and to describe their colours but her eyes either made incessant small movements or else remained fixed as though looking into the distance.

Of the three flowers presented in a row she saw "the blue one in the middle and a red one: the blue one and the red one," neglecting the white one which was to her left. If this was moved she saw it at once.

If asked to pick up the flower which was farthest to her left she picked up the middle one with her left hand although, when asked, she could pick up the flower on the right with her right hand.

Optic ataxia was also observed when she was asked to touch a part of her body. Thus the patient could not use a stick held in the left hand to touch her left or her right great toe to command. Holding the stick in her right hand she was able to do this, although only approximately.

She was asked to fix upon a pin placed in front of her and then close to this pin was placed a lighted match. She perceived both. The same was found in the case of two squares, one blue, the other red, drawn on a sheet of paper and separated by about 4 or 5 cm.

When a series of identical objects were placed in front of her, she saw the two which were immediately in front of her and a third which was a little to the right, but did not seem to notice those placed more laterally.

When asked to enter a room, she did not see the room even when the door was open. She groped about, tended to trap herself between the door and the wall, then inspected the side of the corridor, took hold of the door again, walked round it and again shut herself between the door and the corridor wall.

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Voluntary eye movements.—Asked to look to the right, her eyes wandered about for a moment and finally fixed immediately in front of her. Asked to look to the left there was further wandering of the eyes which only afterwards turned to the left.

If an object was slowly moved to the left she continued to fix upon the examiner without following the object. If the object was moved to the right there were still no pursuit movements. If this was insisted on, jerky movements were obtained and very soon a failure of lateral fixation and a rapid return to the median position.

If an object fixed by the patient was abruptly moved, eye movements did not start until after a certain latent period and were executed without finesse, jerkily and overshooting their mark.

In darkness, slight displacement of fixation towards a point which was suddenly illuminated was observed on both sides. If the patient was asked to follow the light with her eyes, pursuit movements were made fairly easily to the right. When the light returned towards the left the eyes followed it as far as the mid-line position but did not follow it farther left than this central position.

Automatic eye movements were not disturbed, irrespective of whether the object was being fixated or not.

Progress.—The patient left hospital to return to her family. She returned to hospital on 20/10/50. Dementia was obvious. There seemed to be a cortical blindness of which she was unaware. Language disturbances were apparent: paraphasia, amnesia for words, dysarthria of a stammering, stuttering type (logoclonus). Progressive deterioration of her general condition with corresponding increase of dementia and dysphasia. She died 13.12.50.

Post-mortem examination.—Bilateral parieto-occipital astrocytoma with no infiltration of the corpus callosum (fig. 2).

Left hemisphere.—The tumour was limited to the parieto-occipital white matter and extended from the occipital pole, which was infiltrated, to the post-central gyrus, except for the first parietal convolution where the grey matter was involved. The lesion involved all white matter of the angular gyrus and spared the temporal convolutions. The wall of the lateral ventrical was infiltrated; the thalamic radiations were destroyed.

Right hemisphere.—The tumour extended as far as the white matter of the first and second parietal convolutions, spreading towards the region of the grey matter but without actually infiltrating it. It reached forwards as far as the third parietal convolution, thus extending less anteriorly than on the left side. The occipital pole was not involved by the lesion. It extended downwards towards the interventricular foramen. The following were infiltrated by the tumour: the callosal radiations, the thalamic radiations and the inferior longitudinal fasciculus.

Summary.—A woman of 59, who was ambidextrous, showed mild disturbances of language, a left ideomotor apraxia, and apraxia for co-ordinated movements of both hands, apraxia for dressing, marked visual constructive disabilities, "quasi-spatial" acalculia and neglect of the left side of space, particularly noticeable in reading and in counting. There was no evidence of visual agnosia for objects, pictures or colours. There was neglect of the left side of the body, disturbance of spatial orientation and possibly loss of topographical memory.

Elements of Balint's syndrome were: an inability to perceive two objects at the same time in the left visual half-field, a locking of fixation on a particular object (occurring after some initial liability of fixation),

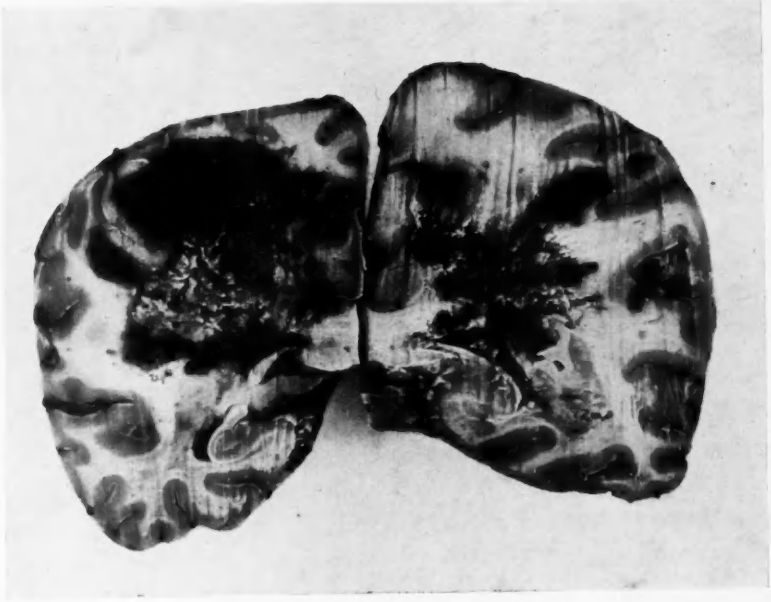

FIG. 2.

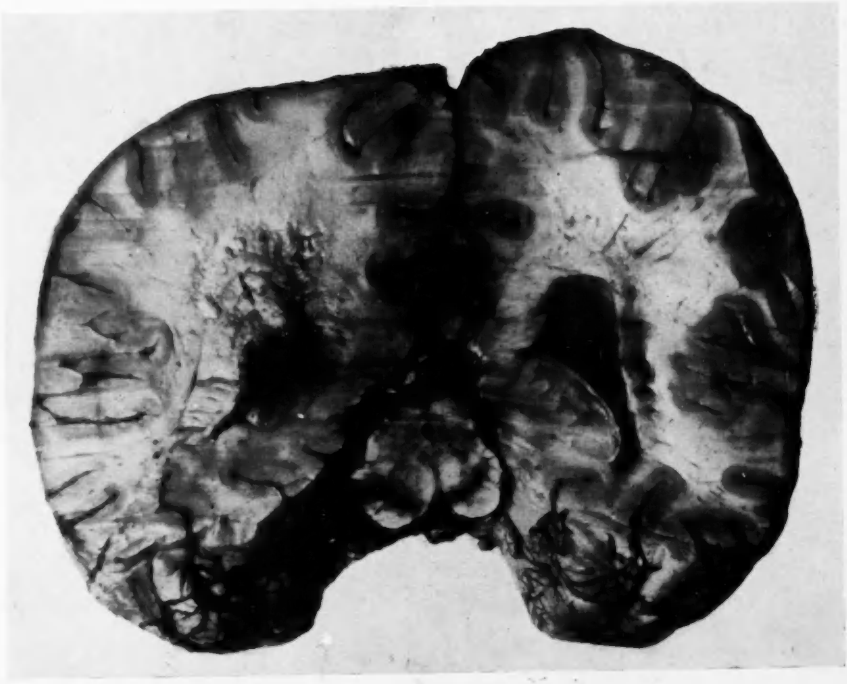

FIG. 3.

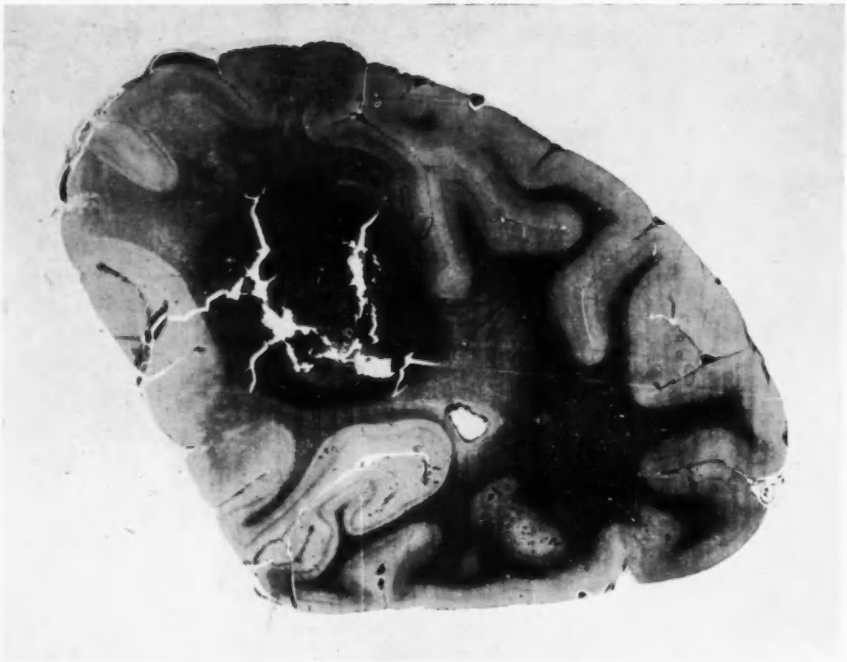

FIG. 4.

FIG. 5.

an optic ataxia and an inability to execute to command the pursuit movements normally involved in following a moving object with the eyes.

Post-mortem examination revealed a bilateral parieto-occipital tumour.

Case 4.—Emile H., aged 55, right handed. Long-standing and gross alcoholism. On January 12, 1953, after an attack of influenza, he suddenly became unable to write, and was unable to use a knife or fork with his right hand. Three days later his family noticed that he could not sit in a chair normally but tended to sit to the side. He became unable to dress and then to feed himself. On about January 25, there were two clonic seizures of the upper limbs. Dr. Colomb, who referred the patient to us, observed rigidity of the neck, paretic signs and a bilateral Babinski response. At this stage the patent showed neither language disturbances nor disorientation and had insight into his disabilities. Shortly afterwards a state of stupor and indifference supervened but the patient could be roused from this. There were word-finding difficulties.

The first E.E.G., on 9.2.53, showed a generalized disturbance of the basic rhythm with intermittent slow anomalies prominent in the posterior part of the left hemisphere. Five days later, the record had become very flat but there were continuous disturbances of mixed type in the left fronto-temporal region.

The patient was examined in our department on 13.2.53. Despite dysphasic difficulties he appeared lucid and well oriented in time and space, but tired very easily.

Motor.—There was right facial paresis of central type. The left arm was held in flexion which was involuntarily increased on forcible extension by the examiner. This state fluctuated, the tone of the flexors suddenly returning to normal, the flexed position, then slowly returning. There was no spontaneous movement in the arm, but there was powerful resistance when asked to oppose passive flexions and extensions.

There was paralysis of the right arm with increase in tone particularly in the extensors, increased reflexes, and wasting of peripheral muscles.

In the legs, apart from extensor responses and increased reflexes, there were no movements. Abdominal reflexes were absent.

Sensory.—No visual field defect could be demonstrated. The fundi were normal.

Results of sensory examination of the arms were inconsistent, sensations being normal in the legs. Faint movement was recognized in the right arm, but there was complete astereognosis. Although the patient failed to feel pain in the right arm, simultaneous pin-pricks were sometimes felt in the right leg and sometimes he said, "I don't know."

Language.—Spontaneous speech showed only occasional paraphasia of which he seemed to be aware. Sentences were short and often incomplete. In conversation, amnesia for words was apparent. On the other hand on naming tests a certain number of objects (spectacles, fountain pen, cigarette, bottle, tie) were named accurately. He had no difficulty in repeating phrases. Simple commands were well carried out. A complicated command (close your eyes, open your mouth, open your eyes, close your mouth and then whistle) was repeated almost correctly, with only one omission, but the patient did not carry out the command.

The patient could read the name of a newspaper. However, if presented with an open newspaper, he had a tendency to read only the headlines on the left. On the other hand he often hesitated for a word and then either stopped or read another quite different word.

Praxis.—The right paresis and the immobility of the upper limb precluded any study of praxis other than bucco-linguo-facial. This, however, was very disturbed and the patient could not, for example, put out his tongue, close his eyes, blow when asked, or imitate facial grimaces performed in front of him. The only responses obtained were generalized movements of the body.

Body perception.—The patient's behaviour with respect to his left side was unusual. Although he moved the left side of his body little if at all, he denied any paralysis. Also he once replied, "My left side is not paralysed but does not want to obey me any more; my right side on the other hand gives me orders," and on another occasion, "My left arm is opposed to my own will." If the examiner's ring was placed on a finger of the patient's left hand, he no longer recognized his hand as his own.

When his hands were crossed and he was allowed to see the examiner move his (the patient's) left hand, he could not say which hand had been moved. Subsequently, he managed to recognize his right hand "by its resistance!" On testing he could point to the examiner's right and left hands. He was able to name parts of his body when these were successively touched.

There were numerous, unsystematic errors in telling the time.

Visual gnosis.—He recognized simple pictures and colours. On Poppelreuter's test he claimed that he saw two strange objects and then identified: a hammer.

There seemed to be a certain amount of neglect of the left side when his recognition of complex pictures was tested. This neglect could be overcome by prompting. However, the patient always gave a mere description of the components, never the meaning of the whole thing. Topographical memory appeared to be preserved (description of a geographical map).

Elements of Balint's syndrome.—In the course of examination, we noticed that the patient never made ocular pursuit movements but always moved his head. If his head was restrained and he was asked to watch an object which was moved either to the right or to the left, only very small eye movements were observed. If objects in his visual field were moved, his eyes did not follow them and the patient sometimes declared, "I lose them; they got lost in the mist." When instructed to look to one side or the other, no eye movements occurred but the patient raised his head without turning it and moved his whole body.

If seven objects were placed in line facing him, he counted five of them. If they were placed in his right half-field, the answer was still five. However, he counted them accurately when they were placed in his left half-field; in this case, his eyes immediately turned to the left.

Some objects scattered randomly on a tray were presented to him. His eyes wandered in all directions and he could only count seven of the ten.

When a cigarette was placed between his lips, he could not bring a lighted match into position to light the cigarette. If a pin was placed before his eyes, he recognized it. A tongue depressor was then slowly moved either from the right or from the left. When this was almost touching the pin, he was asked what he saw. He then accurately described the pin but gave no indication that he had seen the tongue depressor. A similar test gave comparable results: two tongue depressors were placed before him and he acknowledged seeing them. Next he was confronted with a single tongue depressor and then a second depressor was introduced. He continued to see only one, even when the two were very close together.

It is noteworthy that when identical objects were presented in the two half-fields the patient claimed that he could still see the right hand object even when this had been withdrawn, leaving only the left hand object. Similarly, when an object in

the right half-field was replaced by another different object the patient continued to see the first one (paliopsia).

When the patient was fixing an object and this object was moved, a number of jerky eye movements were observed which soon ceased as though despite the subject's efforts, the original fixation could not be disengaged. Passive rotation of the head resulted in normal eye movements opposed to the direction of rotation.

If the patient was asked to watch the movement of a pendulum only a few, very slight eye movements were observed and it was necessary to provide continual prompting. When addressed by the examiner he would turn his head towards him. But if, at this moment, an assistant on the side remote from the examiner gesticulated very close to the patient, the latter showed no reaction either by word or gesture. This effect was present on both the left and the right sides. A loud, unexpected noise, whether on the right or the left, elicited a blink response but no shift in fixation.

Optic ataxia was very difficult to test on account of the motor disabilities. However, when an object was placed within reach of the patient's hand, he grossly overreached and was unable to grasp it.

Progress.—The condition worsened rapidly with increasing dysphasic difficulties and a terminal confusional state precluded further testing. Died 19.2.53.

Post-mortem examination.—Two kinds of lesions have to be considered: vascular lesions in the occipital region and metastatic deposits in the frontal lobes.

Occipital region (fig. 3).—On the right: A hæmorrhage around a metastatic deposit involving an area the size of a nut situated wholly within the white matter of the calcarine gyrus and invading the internal sagittal stratum of Sachs (fig. 4). The hæmorrhage did not reach the calcarine fissure. In the case of the more anterior lesions the hæmorrhage was in the white matter and invaded the occipital horn, cutting the fibres of the tapetum. There was ventricular hæmorrhage. There was softening of the forceps major region.

On the left: There was no hæmorrhage in the occipital pole but the occipital horn was very dilated and filled with a clot of blood. The lesions in the region of the splenium of the corpus callosum involved softening of the whole of the roof and walls of the occipital part of the ventricle. The softening extended upwards as far as the centrum ovale. The forceps major, the superior part of the tapetum and the thalamic radiations were included in the region of softening.

Metastatic lesions (fig. 5).—On the left: a deposit, the size of a large nut, was found in the upper third of the precentral gyrus, and extended forwards as far as the second frontal convolution. There was also a hæmorrhage surrounding the tumour.

On the right: there was a deposit between the first and the second frontal convolutions, but it extended further towards the medial aspect of the first frontal convolution.

The two deposits, on the right and the left, were restricted to the white matter but the right deposit extended as far as the grey matter of the first frontal convolution. They touched the foot of these convolutions but were also observed more anteriorly. A small hæmorrhage was found in the region of the dorso-medial nucleus, inferior to the anterior nucleus. An encapsulated metastatic deposit was found in the left cerebellar white matter. It did not involve the grey matter and spared the dentate nucleus.

Summary.—A patient, aged 55, suddenly developed an agraphia with

apraxia of the right hand. This was soon followed by an apraxia for dressing. Then bilateral paretic signs appeared and finally dysphasic disturbances.

On examination, a right hemiplegia was observed with sensory loss, and paresis of the left leg, a sensory type dysphasia with amnesic difficulties as a prominent symptom. No alexia. There was also bucco-linguo-apraxia. There was lack of spontaneous motor activity on the left side and impaired awareness of the left side of the body. There was some unilateral spatial agnosia. There were definite disturbances of ocular motility, with no spontaneous eye movements and no pursuit movements. There was also difficulty in counting. Having once fixed an object the patient was unable to perceive a second object introduced into his field of vision. Slight optic ataxia was present and definite disturbance of "visual attention" in both half-fields. Visual perseveration (paliopsia) was prominent.

Post-mortem examination revealed bilateral frontal metastatic deposits and bilateral parieto-occipital vascular lesions.

Discussion

These three new observations appear to us to conform with the syndrome described by Balint but it is clear that the individual symptoms are not so marked. Thus the locking of fixation was not absolute. Even some spontaneous movements could occur. The intensity of the disorder increases from Case 2 to Case 4. Similarly, the wandering of the eyes which precedes and follows fixation, is distinctly less marked in all these cases. It should be noted, however, that, in Case 2, the family spontaneously mentioned that they had observed, at one time, an incessant movement of the patient's eyes with inability to fix. The fact that our patients could distinguish two objects presented simultaneously in close proximity and that, in the counting test, they did not confine their exploration to the two or three objects lying strictly in their frontal plane, may be regarded as a direct consequence of the comparative mildness of the primary symptoms. Equally remarkable is the fact that, in Cases 3 and 4, the neglect for the left half of space give a special character to the syndrome, strongly reminiscent of the clinical features of right-sided lesions. In Case 2 this corresponded to a more acute optic ataxia for objects situated to the left. Finally, and perhaps most important, disturbance of visual attention and optic ataxia are much less marked in these minor forms. However, inattention did not extend into other sensory modalities and

so result in a restriction of the patient's whole experience to the frontal plane, as in our Case 1.

The other point which should be considered is that in these cases the syndrome has not the same permanency; it is more variable; it can change from one day to the next; there may be either relapse or remission. However, it is noteworthy that the three essential elements of Balint's syndrome are present in these cases although they vary in degree.

The *concomitant symptomatology* may be more or less marked in so far as the symptoms which reflect damage to the minor hemisphere or to the major hemisphere may be more or less prominent. The most frequently observed disturbances are of the type described in cases of right hemisphere lesions: left unilateral spatial agnosia, apraxia for dressing and lack of spontaneous activity on the left.

Two facts call for special discussion: certain hand postures and loss of co-ordination of the two sides of the body.

In two of our patients we have been impressed by the position and peculiar posture of one of the hands, sometimes the right, sometimes the left. The hand appeared rigid, but relaxed when the patient moved his hand or when his attention was drawn to it. When the movement stopped the hand again became rigid. This should be considered in relation to the ideomotor apraxia or dyspraxia which is often mentioned in published observations. Denny-Brown (1953) has, in fact, emphasized the part played by parietal lesions in the appearance of inhibitory or release effects, effects which he regards as responsible for apraxia. The second point concerns the presence, in cases of bilateral parietal lesions of loss of co-ordination of two parts of the body in the execution of a single act and, particularly, the inability to move the hand beyond the mid-line Hoff and Pötzl (1953); Seitelberger (1953). Thus, our patient 3 could not perform co-ordinated movements with both hands. In patient 1 the situation was different: co-ordination could be accomplished but only under visual control, or after the execution of preliminary movements. Moreover, he could not join his hands unless they were both brought in front of him. In a lateral position either hand might stay in a cataleptic posture. In the case of both vision and proprioception the patient's experience seemed to be restricted to his frontal plane. These effects give the impression either of a subjective dissociation of the body or of a subjective restriction to the mid-line. It is as though a bilateral parietal lesion results in a special awareness (through various modalities) of the disjunction of different parts of the body.

The localization of the lesions.—One fact obtrudes itself immediately, namely that the lesion is bilateral in Balint's and in Holmes's cases as well as in ours. In fact, this bilaterality, as well as being in evidence anatomically, may be affirmed in Case 2 purely on a clinical basis. From the outset this case presented a complete cortical blindness. Similarly, in four unpublished cases observed by Hoff, there were bilateral parieto-occipital lesions.

With regard to the localization of the syndrome, we must refer to Balint's anatomical and clinical observation (bilateral softening). In his case, the lesions involved the left postero-inferior part of the parietal lobe, the angular gyrus, the first occipital convolution and the posterior part of the second temporal convolution. The softening on the right corresponded closely with that on the left, involving a little less of the supramarginal gyrus and the first occipital convolution. Our Case 1 (Balo's type leuco-encephalitis) is, from this standpoint, closely similar, since the lesion involved the parieto-occipital region. In the parietal area most of the lesions were in the first and second parietal convolutions and the angular gyrus. The occipital lesion affected chiefly the convexity of the lobe and, on both sides, spared the lingual and medial occipito-temporal gyri. In addition, there was some damage to the first and second temporal convolutions. The frontal lesions were localized to the third convolution on both sides and an important focus was situated in the second frontal convolution of the right hemisphere.

In our Case 3 only the bilaterality of the lesion may be taken as significant. The whole of the posterior part of both hemispheres may be considered to have been non-functional. In Case 4, as well as the bilateral parieto-occipital lesions, two large metastatic frontal lesions were found. In Hoff's cases the lesions were parieto-occipital.

Holmes (1938) considers that the essential lesions are those which involve the angular gyrus. In our cases, as well as in Balint's, this region was damaged bilaterally. Can we conclude from this that the occipital lesions are not relevant? On the basis of published cases we may at least say that it is not necessary for the medial occipito-temporal and lingual gyri to be involved in order to produce Balint's paralysis of visual fixation. We must at present take note of the bilateral parieto-occipital localization and the involvement of the convexity, and perhaps of the rupture of occipito-frontal associations.

We should not perhaps underestimate the role of the associated frontal lesions which are often observed. In Holmes's view the frontal lesions are responsible for some degree of spasmodic fixation. Indeed, in Balint's

case, there was superior rolandic atrophy on the left side; in our Case 1 the lesions were, as mentioned above, very large and in Case 4 there was a bilateral frontal lesion. Of course, in Hoff and Pötzl's case (1935), in Hoff's cases (1953) and in our Case 2 there is no obvious frontal damage. Perhaps, in these cases, we might suppose that deep lesions produce a rupture of fronto-occipital associations the effect of which may be equivalent to the effect of frontal lesions. We must nevertheless emphasize that the lesions of the prefrontal oculomotor areas are not sufficient to account for this syndrome since, in Case 4, the frontal metastases quite certainly preceded the posterior hæmorrhages and since Balint's syndrome only appeared with the occurrence of the hæmorrhages.

Finally, if we compare the cases which have been anatomically verified and actually published, we may consider on the one hand Balint's case and our Case 1, in which the syndrome was typical and, on the other hand, Hoff and Pötzl's case, and our Cases 3 and 4, where the syndrome appeared in a minor form. Both occipital and frontal lesions were present in both patients of the first group. In the second group it is noteworthy that either frontal lesions are absent (Hoff and Pötzl's case, our Case 3), or posterior lesions involve less destruction (our Case 4).

Perhaps we may then advance the hypothesis that the major syndrome corresponds to very large or plainly destructive lesions involving both occipital and frontal areas. In point of fact, further anatomico-clinical observations are needed before this problem can be resolved.

The first explanation proposed for the syndrome we owe to Balint himself, who spoke of a defect in the spontaneity of attention concerning the "psychological aspect of the visual act." The question as to which disturbance is cause and which effect—oculomotor disturbance or attention disorder—appeared to some authors (e.g. Kleist, 1934) very difficult and even purely verbal. It is therefore necessary to examine these two kinds of explanation. With this in view, we may first consider briefly the cortical control of oculomotility and the effect of its disturbance on perception.

Secondly, in studying the possible sensory effects of the syndrome, the problem of attention again presents itself, but this time at the sensory level. We believe moreover that neither the sensory nor the motor aspects should be neglected and that any attempt to explain these phenomena should take account of their combined disorganization. Indeed an explanation in terms of an attention defect can have only a descrip-

tive value and simply amounts to acknowledging that the disturbance consists of an inability at any particular moment to change the fixation, either automatically or voluntarily, so as to bring any point perceived in peripheral vision into central vision. We have noted, in this connexion, that once a point is perceived, irregular wandering of the eyes usually precedes fixation on this point.

However, this fact does not exclude a defective motor response to the stimulus. It could thus be argued that the restriction of fixation to one point represents a kind of compensatory measure aimed at avoiding the complete spatial disorientation which might otherwise result from the disorganizing effect on perception of the oculomotor disturbance.

Balint's syndrome might then be explained in terms of the oculomotor disturbances. This view of the role of oculomotor disturbances in agnosic phenomena has been held ever since Pieron (1923) and Holmes (1918) discussed the matter. These authors pointed out the importance of ocular reflexes in the perception of space and the part which loss of control of these reflexes must play in spatial disorientations. To admit that oculomotor disturbances play such a role in disturbances of visual recognition would seem to overlook theories of perception which deny any influence from oculomotility.

We know in fact that, according to Gestalt theory, visual perception is something which is immediately given and that the role of eye movements is quite secondary to form perception, being only a placing response. Similarly, Lashley has denied the explanatory value of oculomotor activity in the organization of visual perception. But it seems to us that Hebb's (1949) criticisms of such extreme positions must be borne in mind. Indeed this author, recalling the observations reported by Senden, concerning patients operated on for congenital blindness, shows that visual perception requires prolonged training. Again, Riesen's experiments on chimpanzees reared in darkness provide similar evidence. Hebb also cites, as experimental evidence confirming the role of ocular movements in visual perception, the observations of pseudo-hemianopia described as occurring in monkeys with lesions of the prefrontal oculomotor areas, by Kennard and Ectors, Clark and Lashley. It should be mentioned here that similar disabilities have been observed in man in cases of frontal tumour (Silberpfennig, 1941). On the basis of these facts, Hebb infers that, at least in the child, the role of oculomotility is essential in visual integration, although not itself providing a complete explanation. Also, tachistoscopic experiments show that the perception of pattern involves a "schema with correction," to use Wordworth's term. Similarly, it has been shown that

tachistoscopic reading is much better on the right for subjects who are used to reading in this direction.

All these facts, according to Hebb, suggest that even if the trained adult can perceive without eye movements he can perceive much more clearly and precisely with eye movements. This author believes that the primitive unity of a pattern is certainly something which is innately given; it might be regarded as the bricks and mortar of perception; but eye movements represent the hands of the builder. In fact, the dynamic functions constituting adult vision have to be envisaged as a "sensorimotor circuit."

But before discussing the part played by oculomotor disorders it is, of course, necessary to refer briefly to the cortical areas concerned with oculomotor regulation. It is generally acknowledged that two centres exist: one anterior frontal, the other posterior occipital. The frontal centre situated in area 8 is well defined and does not give rise to any discussion. Moreover, it has little to do with perceptual disturbances, with the exception of the observations concerning frontal pseudo-hemianopia. The occipital centre is not so well defined. Electrical stimulation of the peristriate area of animals by Schaefer, Munk and others elicited ocular movements even after isolation of the occipital lobe, and this eliminates the possibility of the frontal centre being activated by subjective phenomena induced by stimulation. Similarly Walker and Weaver (1940), using the technique of electrical stimulation of the occipital cortex or of the angular gyrus, produced slow deviations of the eyes towards the contralateral side, with or without associated vertical eye movements. These authors point out that, in order to obtain these movements the intensity of the electric current has to be greater than that needed to produce the same movements when area 8 is stimulated. Beevor and Horsley, Minkowski, Biemond and Polyak, on the other hand, have demonstrated the presence of fibres running from the peristriate area to the cerebral peduncle in the region of the oculomotor nuclei.

Whereas the two frontal centres appear to be functionally independent, the two occipital centres are connected through the corpus callosum and appear to inhibit each other in a reciprocal manner. The connexions between the frontal centres and the occipital centres seem to be effected by ipsilateral fibres but the interrelationships of these has not been clearly defined.

Foerster produced ocular movements in man by stimulation of area 19. Penfield and Rasmussen (1950), using more precise electrical stimulation, produced ocular movements only in the frontal area. Using currents of higher intensity, Penfield, in association with Boldrey, obtained movements

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by stimulation of posterior parietal regions. Moreover Kleist (1934), on the basis of architectonic and anatomico-clinical considerations, maintains that an oculogyric centre is present in area 18.

After occipital lobectomy in man, it has been possible to observe contralateral deviations of the eyes and even of the head in the immediate post-operative period (Foerster). More frequently nystagmiform, jerky eye movements, which are often persistent, may be demonstrated. Thus, German and Fox (1934) have shown, by cinematographic recording of the eye movements of a case of left occipital lobectomy, that the eye movements towards the left were slow, jerky and limited in extent. In the cases of occipital lobectomy, performed by Mr. David, which we examined, we identified similar disturbances in the course of clinical examination. These jerky movements can be clearly demonstrated by a graphic record of a patient's eye movements when he is required to follow the movement of a pendulum with his eyes. The clearest case of such a disturbance which we have recorded in this way was a patient in whom Dr. Penfield had removed an epileptogenic focus in the left inferior occipital convexity. The ablation extended to the lingual and medial occipito-temporal gyri. It is noteworthy that the subject himself specifically mentioned that his vision was blurred when he looked to the left. In every case in which we have observed changes of this kind, jerky movements occurred when the eyes were turned towards the side of the cerebral lesion.

The conclusions arrived at by various authors, particularly Fox, allow us to retain the idea that lesions of the posterior parts of the hemispheres (chiefly the supramarginal and angular gyri) have a disturbing effect on optokinetic nystagmus.

Moreover, if it is accepted that optokinetic nystagmus is abolished when the object fixed upon is moved towards the side of the cerebral lesion, there is no need to assume that hemianopia or inattention play any part in the failure to recognize the object visually. Similarly, Fox has pointed out that disturbances of optokinetic nystagmus occurs with frontal lesions and admits that a lesion at any point in the internal sagittal stratum may disturb oculomotor activity.

We may conclude from all these results, which cannot be discussed at further length, that cortical oculomotor areas do actually exist, although their relationships and even their individual functions have not been fully elucidated.

Gordon Holmes, who believed in the importance of bilateral lesions of the angular gyrus in determining this syndrome (which we equate with the syndrome described by Balint) wrote: "One of the functions of this part of the brain is the reflex adjustment of the eyes to the peripheral

stimuli or the co-ordination and integration of the afferent impressions which, through those efferent centres, evoke appropriate ocular movements in response to the retinal excitation." In this way, these lesions might easily explain the wandering eye movements when the patient attempts to fix. The bilaterality of the lesion would seem to be an essential condition for the appearance of "locking" of fixation. Indeed, the frontal oculomotor centres exert an inhibiting effect on the occipital centres. In the case of a unilateral posterior lesion, this effect can always be exerted since the occipital centres are interconnected. However, in the case of bilateral lesions, frontal co-ordination of oculomotor activity and visual stimuli becomes impossible. Fixation is then wholly determined by the effects of ocular and general proprioception. After the irregular eye movements which occur when an object falls in the central field of vision, the resultant proprioceptive activity will have its effect on the frontal field. There will, however, be no way in which visual data can counteract this effect.[1]

Hence persistence of fixation and, in so far as this is something more than a sensory disorder, limitation of the peripheral visual field might also exist. Moreover, Holmes has particularly emphasized the role of the afferent impulses from the ocular and neck muscles in the localization of objects in relation to the body. According to this view, visual stimuli can provide only two dimensional images but spatial localization depends on the co-ordination of visual and proprioceptive functions, and this co-ordination may be regarded as the physiological correlate of the psychological judgment concerning positioning in space.

The association of optic ataxia with "psychic paralysis" may thus be explained unequivocally: it is a manifestation of the disorganization of the mechanism of sensorimotor connexions which is essential for the integration of spatial orientation. In this way we may explain the errors of visual estimation of the distance of an object which are apparent in the behaviour of patients suffering from "psychic paralysis."

Since the vestibular system is important in the integration of oculomotor proprioception the relevance of disturbances of this system must also be considered; thus Case 1 showed clear vestibular disturbances.

[1] In this context it is worth pointing out the phenomena of visual perseveration found in Case 4. In a previous paper it was suggested that locking of fixation might represent a defence mechanism aimed at avoiding the complete disorientation which could result from an inability to fix at all. We suggested that the object fixed, even after it has vanished from sight, is perhaps still used as an actual point of reference, on the basis of the spatial characteristics of proprioception which has become associated with the object. Visual preservation might then arise from this mechanism.

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Apart from discussions as to the existence of vestibular "centres," it can be said that lesions at the cortical level may produce vestibular disturbances. These disturbances often take the form of perceptual distortions of the metamorphopsia type and deviations of the apparent vertical and horizontal. There may even be actual impairment on tests of vestibular functions, although always to a lesser degree than is the case in subcortical lesions. In our experience it is chiefly in cases of posterior parietal lesions that such is found. In a former study of lesions of the right hemisphere, Hécaen, Ajuriaguerra and Massonnet (1951) drew attention on the one hand to metamorphopsia, topographical disturbances and objective vestibular disturbances, and on the other hand to visual constructive disabilities. In addition we should mention the frequency, in these syndromes, of spatial disorientation and neglect of the left half of space. There is thus a possibility that cortical vestibular impairment influences perception and that these disorders are associated with oculomotor disturbance.

Although we have attempted to give an explanation essentially in terms of oculomotor disturbance, the influence of sensory factors must still be considered. Also, from the psychological point of view, any discussion of the role of attention suggests a sensory background. Can this line of reasoning be carried further without losing touch with physiological considerations?

According to Gelb and Goldstein's studies, a concentric narrowing of the visual field is produced when one part is subjected to prolonged excitation. These authors, like Stein, observed that the "fatigue" of the stimulated region can irradiate into unstimulated regions. Thus, we might say that if, in cases of Balint's syndrome, a narrowing of peripheral vision does exist then successive stimulation of this region produces "fatigue" which tends to extend towards the central field and which causes the patient to react with multiple ocular excursions. That might be the sole reaction and, in that case, we are confronted with the clinical picture of blindness for place described by Kleist. This author considers that side by side with the disturbance of peripheral vision, which prevents any exploratory eye movements away from the point of fixation, there is also a weakness of central vision or weakness of fixation, whereby an object previously fixed is lost, and is fixed upon again only after trial and error eye movements. But, if central vison is not "fatigued," there would, on the contrary, be locking of fixation on to the object in question without any possibility of further lability of eye movements. Any attempt to shift fixation will result in the same peripheral fatigue and a rapid return of fixation to the mid-line. This will have the obvious result of a narrowing

of attention, the patient tending to avoid the disorganizing effect of the disturbance.

Thus we could say that weakness of peripheral fixation, together with reduction of central vision in Kleist's sense, are the essential conditions which prevent continuous fixation, whereas weakness of peripheral vision alone would result in the Holmes type of spasmodic fixation. As regards the necessary conditions for such a reduction of peripheral vision, the explanation may lie in the local oscillations of the threshold of excitability, as suggested by Stein.

Seen in this light, the question should be considered in relation to the phenomena of extinction. Is it not possible that both peripheral fields are subject to these disturbances, that a bilateral pseudo-hemianopia may occur in some such fashion?

It is not proposed to discuss in detail the nature of this phenomenon of extinction but it is interesting to recall that Denny-Brown has recently postulated a similar physological explanation for the cases of disorientation reported by Holmes. According to Denny-Brown, such disorientations consist of a bilateral amorphosynthesis and should be distinguished from the truly agnosic phenomenon of loss of topographical memory. Denny-Brown understands amorphosynthesis to be a defect of the spatial significance of sensation. A patient suffering from a parietal lesion no longer has an adequate spatial discrimination with respect to sensation on the side contralateral to the lesion. The threshold of spatial summation is raised and the patient is unable to synthesize multiple sensory data. This explanation can thus account for these patients' perceptual disturbances, but cannot be applied to the oculomotor disorders shown by them, unless these disorders are regarded as equivalent to the unconscious motor reactions which Denny-Brown observed in patients with parietal lesions showing amorphosynthesis. In his view these phenomena of avoidance and instinctive prehension, of visual or tactile origin, represent release or facilitation phenomena. He has also observed them in animals after parietal ablation. For this author they are true apraxias. With regard to Balint's syndrome, is it justifiable to extend his interpretation and to regard the lability of fixation, as well as spasmodic fixation, as motor responses which are released or facilitated by a lack of sensory stimuli and by overactivity of other classes of stimuli, the effect of which is compensated for under normal conditions? In this context it should be mentioned that in our patients it was possible to observe curious hand postures comparable to what has been described by Denny-Brown, Meyer and Horenstein (1952). May we conclude that these reactions in the hand originate in the same way as the oculomotor disturbances? This must remain in doubt.

Whether sensory or oculomotor factors predominate in determining Balint's syndrome, we have already suggested in 1950 that the following mechanism might underlie the syndrome: initial lability of fixation in searching for an object, quasi-involuntary fixation and, finally, consistent locking of fixation, this last effect constituting a defence mechanism or, to use Holmes term, spasmodic fixation.

It seemed to us essential not to make an arbitrary distinction between the wandering eye movements and spasmodic fixation on the one hand and sensory mechanisms and oculomotor mechanisms on the other, since the final behaviour pattern represents an attempt to adapt to, and compensate for, the functional disorganization which affects both components. This disorder is reminiscent of the primitive behaviour which is found when a function is not yet fully integrated. This can be seen in human infants during the first few months of life when ocular motility and sensory differentiation have not fully matured. It has already been pointed out that there is an affinity between this oculomotor phenomenon and the phenomenon observed in another sphere of psychomotor activity. In both the behaviour is "captured" by the object as a result of the proprioceptive consequences of the behaviour. The grasp reflex for instance seems to us to merit such comparison. Not only does it represent a certain stage in the integration of motility but also it gives a clue to the extreme importance of proprioceptive, tactile and sometimes visual afferent impulses in the facilitation of the voluntary act. Clearly, disintegration does not result in exact repetition of stages reached in the course of integration. Instead, simply as a result of a cerebral lesion, we are presented with functional fragments which are more primitive and less voluntary than normally. In this way certain aspects of infantile behaviour will colour the picture, but in the setting of otherwise adult behaviour.

Although various mechanisms may modify Balint's syndrome, it seemed of interest to point out the possibility of minor forms. Such minor forms, apart from the opportunities for semiological study which they provide, have practical importance in demonstrating the relevance of bilateral lesions.

The anatomical reasons for this difference in symptomatic intensity cannot be stated in any definite way.

Summary

(1) The syndrome described by Balint in 1909 contains three essential elements: psychic paralysis of the visual fixation, optical ataxia and disturbance of visual attention. There exist very few observations of this syndrome in its complete form; they are briefly reviewed.

(2) In the psychic paralysis of the visual fixation itself, we are of the opinion that two phases must be distinguished; first the wandering of the visual fixation in search of the object, followed by its secondary fixation once the object has been met by chance.

(3) Three new cases, two of which are anatomo-clinical, are presented here, but they are minor forms of this syndrome. The three elements cited above are nevertheless present but in an inconspicuous or transitory form. Their presence, however, allows the differentiation from cases of simple spasmodic fixation.

(4) The symptoms that often accompany this syndrome are recalled, especially certain tonic and motor phenomena of the upper extremities on the one hand, and the loss of co-ordination of the two parts of the body on the other hand.

(5) Judging from the anatomo-clinical cases in the literature and from our own personal cases, we think that, in the presence of Balint's syndrome, even in its minor form, the bilaterality of the lesion may be affirmed. The injury to the parieto-occipital regions seems constant. Rupture of the parieto-occipital connexions may also be one of the necessary conditions for the production of the syndrome. Finally, the part played by the frontal lesions must not be underrated in the formation of the complete syndromes.

(6) The various theories proposed to explain this syndrome are discussed: deficit of the spontaneity of attention, oculomotor disturbances, disturbance of perception. It seems essential not to oppose sensory and oculomotor mechanisms in the pathogenesis of this disorder and to look upon the demeanour of the subject as an attempt to adjust himself and counterbalance the disorganization of the function, disturbed in its two components.

We wish to express our thanks to Mr. Piercy who has been kind enough to review the English text.

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PHYSIOLOGICAL PROCESSES RELATED TO CONSCIOUSNESS AND PERCEPTION[1]

BY

E. GELLHORN

(From the Laboratory of Neurophysiology, Department of Physiology, University of Minnesota, Minneapolis, Minnesota)

It may be correct as E. du Bois-Reymond pointed out long ago that the physiological investigation of cerebral processes does not contribute to an understanding of the essence of psychological processes. Nevertheless, the study of the physiological processes which accompany certain psychic events is of greatest interest to physiology, psychology and psychiatry regardless of the relation which exists between physiological and psychological phenomena. Studies made on man and experimental animals have definitively established that certain psychic changes are invariably connected with lowering of the oxygen tension of the inhaled air, with the diminution of the glucose concentration of the blood and with the administration of certain drugs.

Clinical observations have added a wealth of information about this physiological-psychological relationship. It may suffice to mention the changes in the electroencephalogram, associated with a lapse of consciousness, the production of manic symptoms by the mechanical stimulation of the hypothalamic area (Foerster), and Penfield's observation that electrical stimulation of the temporal lobe in the conscious patient evokes the recollection from past experience of a whole chain of events.[2]

Decades of brain research have shown that such apparently simple problems as the interpretation of a cerebral lesion leading to a motor deficit are very complex. This holds true to an even higher degree when the relation involved is that between brain function and sensory processes. For this reason it seems advisable to approach the problem of psycho-

[1] These studies were aided by a contract between the Office of Naval Research, Department of the Navy, and the University of Minnesota and by the Louis W. and Maud Hill Family Foundation.

[2] Concerning the literature and further details of the problems discussed in this paper see: E. Gellhorn. *"Physiological Foundations of Neurology and Psychiatry,"* Part III. The Physiological Basis of Consciousness.

physiological relations by determining the physiological conditions which are associated with the simplest psychic processes.

Perhaps the most primitive psychic phenomenon is what may be called awareness. Coma, sleep, wakefulness, and attention indicate increasing degrees of awareness corresponding to responses of different degrees to arousal stimuli of varying intensity.

In the waking organism the effect of sensory stimuli is widespread, involving apparently the whole cortex. In the unconscious (i.e. deeply anæsthetized animal) the effect of such stimuli is restricted to the specific cortical projection area. A fundamental question, therefore, regarding the physiological basis of consciousness is: What mechanism accounts for this alteration in the effect of afferent stimuli on the cerebral cortex in different states of consciousness?

To the writer it seemed likely that the hypothalamus plays an important role in awareness for two reasons: first, because stimulation of this structure in the unanæsthetized animal leads to arousal reactions and, with greater intensities of stimulation, to signs of psychomotor excitation (Hess, 1947). Secondly, stimulation of the hypothalamus causes a generalized excitation of the cerebral cortex, indicated by asynchronous discharges (Murphy and Gellhorn, 1945), and nociceptive stimuli having similar effects on the cortex produce signs of excitation of the hypothalamus (Gellhorn and Ballin, 1946).

A more detailed study revealed that in "light" anæsthesia in which spontaneous movements and blinking occurred, nociceptive, proprioceptive, or acoustic stimuli elicited a generalized cortical excitation which was accompanied by overt signs of awakening. In "deep" anæsthesia nociceptive stimulation produced a generalized cortical excitation, whereas proprioceptive or acoustic stimuli failed to do so. Nociceptive stimulation was in general found to be more effective than proprioceptive stimuli (Bernhaut, Gellhorn and Rasmussen, 1953). As fig. 1 shows, a more prolonged generalized excitation results from nociceptive than from proprioceptive stimuli, and in the same state of anæsthesia acoustic stimuli affect only the auditory cortical area. The important fact that generalized cortical excitation is accompanied by hypothalamic excitation whereas hypothalamic excitation does not accompany the specific activation of the auditory projection area is also shown in the figure. This correlation was found to be valid in numerous experiments. From them it was inferred that arousal is due to a hypothalamic-cortical discharge which affects the cerebral cortex as a whole. With deepening anæsthesia arousal is less easily effected, hypothalamic excitation disappears, and the cortical response becomes restricted to the specific sensory projection area.

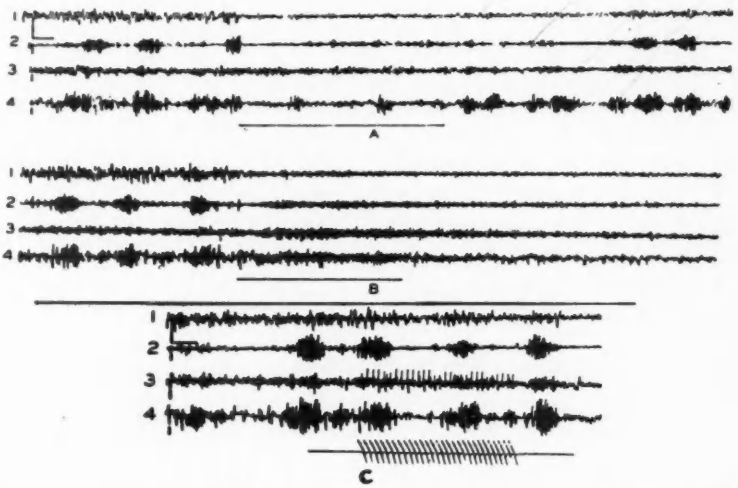

FIG. 1.—"Moderately light" cat, 24 hours after dial-urethane. 1, left lateral mammillary nucleus; 2, left sensorimotor area; 3, left primary auditory area; 4, left optic area. A, Partially generalized cortical response with activation of posterior hypothalamus in response to proprioceptive stimulation. Excitation in lateral mammillary nucleus, sensorimotor and optic areas and no excitaton in auditory area. B, Generalized cortical response with activation of posterior hypothalamus in response to nociceptive stimulation. C, Specific response of auditory cortex to acoustic stimuli indicated in bottom line.

The posterior part of the hypothalamus was largely involved in these reactions (Murphy and Gellhorn, 1945; Bernhaut, Gellhorn and Rasmussen, 1953). When a lesion was produced unilaterally in this area, the nociceptive effect on the cortex was mainly confined to the side of the intact hypothalamus (Koella and Gellhorn, 1954). Since unilateral lesions of the posterior hypothalamus are associated with greater prominence of the slow, grouped ("Dial"-) potentials, it may be said that the posterior hypothalamus exerts a *tonic* influence, particularly on the ipsilateral cortex, and that *phasic* effects in its "upward discharge" are produced by afferent stimuli. Both tonic and phasic reactions seem to determine the level of awareness.

If it be true that awareness depends primarily on the intensity of the hypothalamic-cortical discharge, it is to be expected that drugs and procedures which chiefly affect the diencephalon, and consequently the degree of hypothalamic "upward" and "downward" discharges, would alter the state of awareness. In order to determine this point a first group of experiments was undertaken on the action of low and high concentrations

of carbon dioxide. Schäfer (1949) had observed that 3 per cent CO_2 produced symptoms indicative of psychomotor excitation if the experimental subject remained in a room containing 3 per cent CO_2 for several hours. CO_2 in high concentration, on the other hand, is a narcotic able to abolish consciousness within a few minutes. The influence of low and high concentrations of CO_2 (Gellhorn, 1953, *a* and *b*) on the hypothalamic-cortical discharges was consequently made the focus of investigation, these discharges having previously been shown to parallel the state of awareness. It was found that CO_2 in relatively low concentrations[1] causes an excitation of the hypothalamus and cortex which is characterized by the usual signs of increased asynchrony in the potentials: grouped

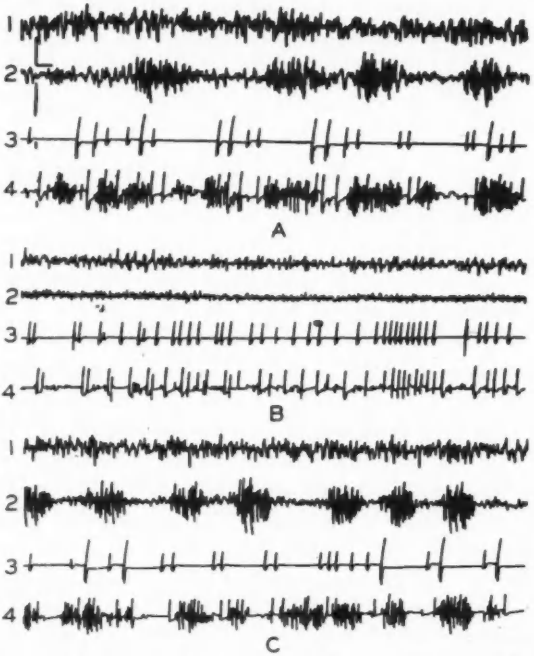

FIG. 2.—Effect of 10 per cent CO_2 on hypothalamus and cortical potentials in a cat anæsthetized with Pentothal. 1, R. hypothalamus; 2, L. motor cortex; 3, L. occipital cortex, strychninized; 4, R. occipital cortex, strychninized. A, control in air; B, after 2′ in 10 per cent CO_2; C, 3½′ after air had again been administered. Calibration 300 μV. and 1″.

[1] In anæsthetized animals higher concentrations are needed to show these effects than in unanæsthetized human subjects. Moreover, the effect of CO_2 is the result of concentration and time (Schäfer, Cornish, Stuntz, Lukas, Brewer and Carey, 1952) so that in brief experiments higher concentrations are required. For our purposes 10 per cent CO_2 is "low," 30-40 per cent is "high."

potentials disappear and are replaced by small and more frequent "background" potentials. Moreover, when strychnine spikes (induced locally by the application of strychnine to a cortical site) were recorded it was found that their frequency increased during the inhalation of "low" CO_2 (fig. 2).

Three series of experiments have been performed in this laboratory which suggest that these changes are due to increased hypothalamic "upward" discharges: (1) It has been shown that CO_2 increases the frequency of convulsive cortical discharges (strychnine spikes) only when the cortex can receive impulses from subcortical structures. If two cortical sites are strychninized and one of them is undercut, the normal cortex shows an increase and the operated cortex a decrease in the rate of convulsive discharges on inhalation of "low" CO_2 (Gellhorn and French, 1953). (2) The effectiveness of nociceptive and proprioceptive impulses which have been shown to induce a hypothalamic-cortical discharge is increased in "low" CO_2. (3) Ipsilateral lesions in the posterior hypothalamus reduce or abolish the generalized CO_2-induced cortical excitation at the side of the lesion (Koella and Gellhorn, 1954).

Only one of these effects of carbon dioxide is illustrated in fig. 3. It is

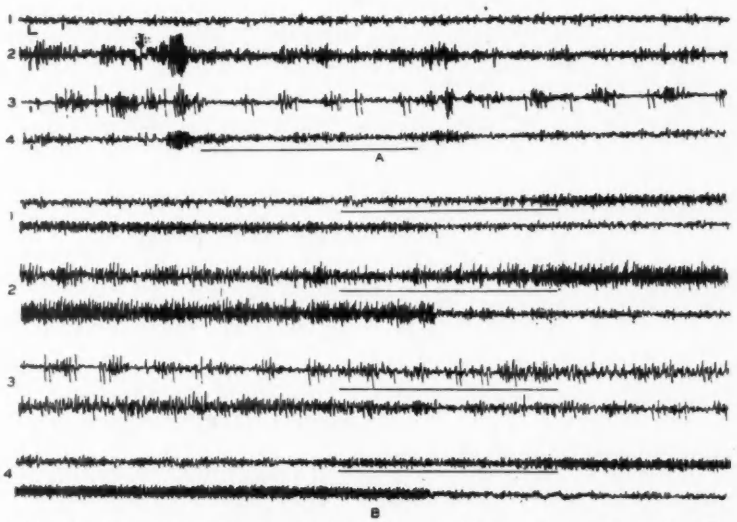

FIG. 3. Cat, pentothal anæsthesia. Effect of 10 per cent carbon dioxide on nociceptive stimulation (immersion of right hind leg in water of 60° C. for 25 seconds). 1, right hypothalamus; 2, left motor cortex; 3, left gyrus suprasylvius; 4, right motor cortex. A, control, i.e. nociceptive stimulation prior to carbon dioxide. B, nociceptive stimulation during inhalation of 10 per cent carbon dioxide. The records of the B group start two minutes after the onset of hypercapnia. The records shown under each number in section B are continuous.

shown that the intensity of the hypothalamic and cortical excitation resulting from nociceptive stimuli is greatly increased during the administration of CO_2. Not only are the cortical and hypothalamic discharges markedly accelerated but the amplitude of the potentials is increased, an effect believed to be due to the recruitment of neurons previously not active. It may be added that nociceptive stimuli of subthreshold intensity may become effective under the influence of "low" CO_2.

When CO_2 is applied in high concentrations (30-40 per cent), consciousness is lost rapidly. Under these conditions it may be considered to be an anæsthetic substance. In the experimental animal, the hypothalamus and cortex show changes in potentials which indicate a lessened excitability, except for the first minute, when excitatory phenomena prevail. After that the frequency of these potentials decreases and the tendency toward synchrony increases. Fig. 4A, which presents records taken immediately after administration of 35 per cent CO_2, shows the early excitatory phase in which hypothalamic and cortical potentials increase in frequency and grouped potentials disappear (asynchrony). B, taken a little later, shows how the potentials decrease in frequency and may even disappear from the

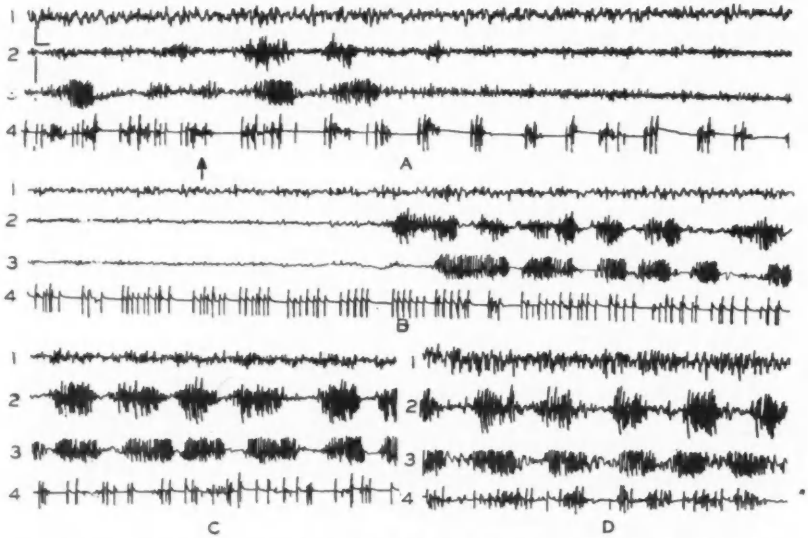

FIG. 4.—Effect 35 per cent CO_2 on hypothalamic and cortical potentials. A, control and beginning of CO_2 period at the arrow; B, 3′ in CO_2; C and D, 1 and 34′ respectively after readministration of air. Cat, pentothal anæsthesia. 1, r. hypothalamus; 2, l. motor cortex; 3, r. motor cortex; 4, r. occipital cortex; calibration: 300 μV. and 1″.

cortex. From this depressant action a partial recovery may occur: the potentials reappear and increase in amplitude while the tendency to synchrony as indicated by the appearance of large grouped potentials is greatly increased.[1] These grouped potentials persist during the subsequent control periods (C, D.).

Animals which are in a state of "light" barbiturate anæsthesia show these grouped potentials to a small degree. They are separated from one another by smaller and more frequent "background" potentials. "High" CO_2 influences these two types of potentials differentially: the grouped potentials appear more often while the background potentials are greatly diminished or abolished. This is clearly seen by comparing hypothalamic and cortical potentials recorded during the inhalation of 40 per cent CO_2 with the potentials noted in the preceding and following control period, when air was inhaled (fig. 5). In addition it is seen that proprioceptive

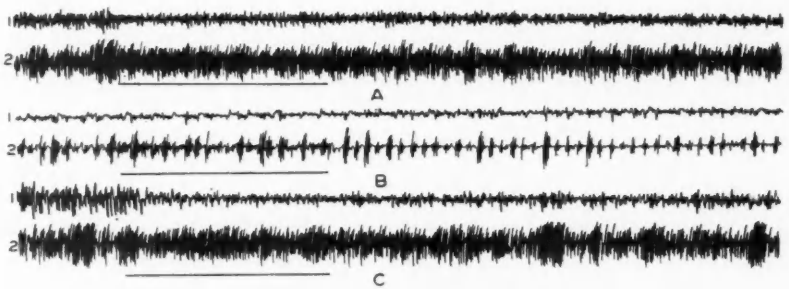

FIG. 5.—Effect of proprioceptive impulses (rhythmic movements of right hind-leg during period of stimulation) on potentials of l. hypothalamus (1) and l. motor cortex (2) during control (A), after 4′ in 40 per cent CO_2 (B), and 4′ after restoration of air (C). dial cat. Period of stimulation in figs. 5–6 indicated by horizontal line.

stimulation is ineffective during the administration of 40 per cent CO_2 (fig. 5B) whereas a profound excitatory effect which outlasts the period of stimulation for a considerable time occurs during the control periods (fig. 5, A and C).

Fig. 6 gives another example of the fundamental changes which occur in hypothalamic and cortical potentials during the inhalation of "high" CO_2. The greater prevalence of grouped potentials and the absence of "background" potentials is easily recognized. It is further seen that the excitatory effect of nociceptive stimulation is abolished under these conditions.

[1] A similar recovery is seen in cortical potentials during anoxia, induced by lowering of the barometric pressure Kessler, Hailman and Gellhorn, 1943).

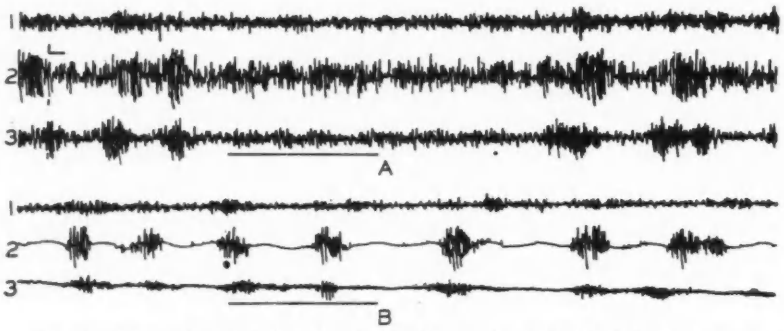

FIG. 6.—Effect of nociceptive stimulation (immersion of r. hind-leg into water of 70° C. for 10″) on potentials of r. hypothalamus (1), l. motor cortex (2), and l. gyrus suprasylvius (3). A, control; B, 70″ after administration of 30 per cent CO_2. Calibration 100 μV. and 1″. Penthothal cat.

The effects of "high" CO_2 on brain potentials and on signs of awareness seem to be interrelated. With deepening anæsthesia the background potentials are lessened and at the same time the grouped potentials become more prominent. Moreover, the responsiveness to proprioceptive and nociceptive stimuli which activate the hypothalamic-cortical system is reduced or eliminated. The failure of the hypothalamic-cortical system to react to nociceptive or proprioceptive stimuli is paralleled by the absence of overt signs of arousal.

Similar changes in hypothalamic and cortical potentials are observed in barbiturate anæsthesia. Moreover, it is found in the anæsthetic state that the generalized reactions to nociceptive stimuli are abolished whereas the excitation of specific cortical projection areas to acoustic and optic stimuli persists (Gellhorn, 1953*c*).

It is interesting to add that at the hypnotic stage of barbiturate anæsthesia the patient is euphoric and talkative and the cortical potentials show an increase in frequency (Tucci, Brazier, Miles and Finesinger, 1949). It is suggested that the diminution of cortical functions at the early stages of barbiturate anæsthesia leads to a release of the hypothalmus[1] and later, as the anæsthetic affects also the subcortical structures, to a depression of its functions. The former state is associated with an increased hypothalamic-cortical discharge and increased psychomotor activity, the latter with a diminished discharge and attendant loss of consciousness.

In summary of the data thus far presented, it may be said that low

[1] cf. also the release of the hypothalamus in anoxia which may lead to synchronous convulsions in cortex and cerebellum after injection of strychnine into the hypothalamus (Gellhorn, Ballin and Riggle, 1951).

concentrations of CO_2 increase psychomotor activity and augment hypothalamic-cortical discharges. These effects on behaviour and cortical potentials may be imitated by stimulation of the posterior hypothalamus in the unanæsthetized animal. On the other hand, the administration of high concentrations of CO_2 as well as that of barbiturates leads to a state of diminished hypothalamic activity; sleep or coma is induced; and the hypothalamic-cortical discharges are diminished correspondingly.

By a somewhat different approach than ours Magoun, Lindsley, French (French and Magoun, 1949; Lindsley, Bowden and Magoun, 1950; Moruzzi and Magoun, 1949) and their collaborators have made fundamental contributions to the physiology of awareness. They have shown that the arousal induced by various stimuli and leading to a generalized activation of the cortex is associated with the excitation of the reticular system. Lesions of this reticular system lead to coma in cats and monkeys, whereas similar lesions in the lateral parts of the brain-stem that interrupt the classical projection systems to specific cortical areas do not interfere with normal posture and behaviour. In animals with lateral brain-stem lesions, moreover, the cortical potentials are normal and change into small fast potentials on minimal sensory stimuli.

It follows from these observations that the cortex receives at least two kinds of afferent impulses, those which alter the activity in the greater part of the whole of the cortex and those which activate specific cortical projection areas (visual, auditory, etc.). The former involve Magoun's reticular system of which the hypothalamus is a part. The role of the hypothalamus has been emphasized in our studies because of its significance for *reversible* changes in the state of awareness, a significance well established through the work of Hess, Ranson and others (*see* Gellhorn (1953*d*) for literature).

French, Verzeano and Magoun (1953) have likewise studied the influence of barbiturates on these two afferent systems and have come to conclusions similar to those of the writer (Bernhaut, Gellhorn and Rasmussen, 1953, Gellhorn, 1953*c*). They found that barbiturates depress the conduction via the reticular substance to the cortex, whereas that involving the specific sensory pathways is unimpaired.

These investigations are of great interest not only for the problem of awareness but also for an understanding of the physiological mechanisms underlying sensation and perception. It has been known for a considerable time that when the animal is in deep narcosis and the spontaneous electrical activity of the cortex is greatly reduced, minimal sensory stimuli evoke potentials restricted to a small part of a specific cortical sensory projection area. It may be inferred from these observations that

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cortical responses in a projection area occur in conditions which certainly exclude the presence of a sensation or perception.

The present discussion is not concerned with the numerous complexities involved in even the simplest sensations and perceptions.[1] It does not consider the important and difficult problem of how the spatial and temporal stimulus pattern is transformed into a pattern of cortical excitation which leads to the perception of the stimulus object (cf. Lashley, Chow and Semmes, 1951); nor does it attempt to clarify whether more than one projection area must be activated in order to produce a sensation.[2] All we wish to determine are the necessary although by no means sufficient conditions without which a sensation cannot occur.

The observations presented in this paper show:

(1) That awareness depends on the reticulo-hypothalamic-cortical system.

(2) That the excitation of a specific cortical projection area such as the visual area may adequately function (i.e. respond to minimal optic stimuli) in deep coma.

Apparently elimination of the specific afferent systems, while not depriving the organism of awareness as such, abolishes the source of information from the outside world which forms a very important part of the content of consciousness. On the other hand, destruction of the reticulo-hypothalamic system does not interfere with the action of the sensory impulse on a specific projection area but it eliminates the tonic impulses from the hypothalamic-reticular system on the cortex as a whole. Under these conditions no conscious processes are elicited. From this it seems to follow that a simple conscious process such as the sensation of a colour or the perception of an object requires the presence of both systems.

These findings raise the question of how the two afferent systems interact. If deeply anæsthetized cats are used it can be shown that the sensory (acoustic) response is not grossly altered when the hypothalamic-cortical discharge is increased (Gellhorn, 1952). However, more detailed experiments have shown that a definite interaction between impulses elicited in the two systems takes place. This may be demonstrated by two methods.

In the first the effect of activating the hypothalamic-cortical system through nociceptive impulses was studied on the response of the cortex to

[1] The writer does not distinguish sharply between sensations and perceptions but assumes with Graham (1951) that "perception is an aggregate of sensations."

[2] Fischer (1952) calls attention to the fact that even such a primitive sensation as a photoma is a perception with relation to the body image and probably involves parts of the cortex outside of the area striata.

acoustic or optic stimuli (Gellhorn, Koella and Ballin, 1954). In experiments with near threshold sensory stimuli the percentage of auditory or visual responses increased during nociceptive stimulation. If potentials were recorded from several cortical sites within the same projection area (e.g. auditory cortex) sensory responses appeared during nociceptive stimulation at cortical sites which did not react in the absence of nociception. These effects were particularly marked after strychninization of a cortical site. Fig. 7 shows that under control conditions, in response to acoustic stimuli, small auditory potentials appear in Nos. 2 and 3 (fig. 7B) whereas following

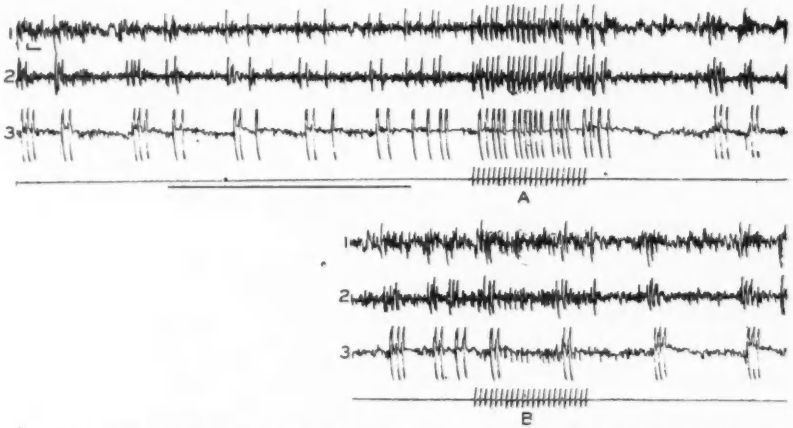

FIG. 7.—Effect of acoustic stimuli at 2·3/sec. on two cortical sites located in the left auditory area (records 1 and 2) and on site of the right auditory area (record 3, strychninized). In part A nociceptive stimulation (immersion of right hind-leg in water of 55° C) is applied during the time indicated by the long horizontal line and is followed by acoustic stimuli indicated by the signal magnet. Part B shows the effect of acoustic stimulation under control conditions. Calibration: 100 μV. and 1 second. Cat was operated under local anæsthesia and intocostrin.

nociceptive stimulation large convulsive spikes appear at all three sites. It is worthy of mention that this stimulation occurs even though the nociceptive stimulus was so weak that it did not significantly alter cortical potentials.

Since the diffuse cortical effects resulting from nociceptive stimulation have been shown to involve the hypothalamic-cortical system, these results were interpreted to indicate that impulses of a classic sensory system interact with those of the hypothalamic-cortical system. A second, more direct, procedure was applied to re-investigate this problem. Experiments were performed to decide the question whether the stimulation of the hypothalamus would likewise increase the cortical response to acoustic or

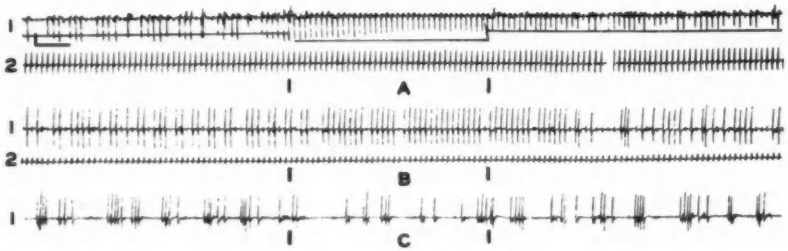

FIG. 8.—Cat, anæsthetized with nembutal. 1, visual projection area; 2, optic stimulus. Fig. 8A and B showing the effect of hypothalamic plus optic stimulation. Note that the intensity of the optic stimuli is reduced in Fig. 8B. Hypothalamic stimulation without optic stimuli is applied in Fig. 8C. The site of the hypothalamic stimulation is lateral and just anterior to the right mammillary body.

Increase in optical response occurs under the influence of hypothalamic stimulation (A and B), although the latter, when applied alone (C), reduced the number of spikes.

optic stimuli. This was found to be true (fig. 8).[1] It may be concluded that discharges following direct or reflex excitation of the hypothalamus interact with impulses reaching the cerebral cortex via the specific afferent systems. Although the site of this interaction has not yet been determined, the interaction appears in an intensification of the cortical sensory response and also in an increase of the cortical area from which it may be recorded. These phenomena may be related to the qualitative alteration of sensations under the influence of emotion.

The studies reported in this paper seem to throw some light on work based on electroencephalographic recordings in man. It is well known through numerous investigations that the alpha potentials of the electroencephalogram disappear under the influence of tension and emotion (anxiety). Similar changes occur as the result of visual attention. When the attention is shifted from vision to audition, Adrian (1947) showed that the alpha potentials reappear in the occipital electroencephalogram. These phenomena suggest that hypothalamic-cortical discharges are increased in emotional excitement and that minor and more localized changes in the intensity of this discharge occur in the state of attention. The decreasing areal extent of cortical excitation which occurs on hypothalamic excitation in progressive degrees of barbiturate anæsthesia (Bernhaut, Gellhorn and Rasmussen, 1953; Gellhorn, 1953c) which was mentioned earlier may serve as a model for relatively restricted cortical effects of hypothalamic discharges during attention.

Electroencephalographic studies on infants lend further support to the

[1] *See* Gellhorn, E., Koella, W. P., Ballin, H. M., *J. Psychol.* In press.

idea that hypothalamic-cortical discharges are involved in attention and emotional excitation. The visual blocking of alpha potentials is absent in young infants although resting brain potentials can be recorded. These potentials show a much greater variation in frequency than in the adult brain. It may not be unreasonable to assume that under the influence of hypothalamic-cortical discharges the cortical potentials increase in frequency and areal differences disappear. These differences persist in behaviour problem children characterized by emotional immaturity and reappear in adults in barbiturate poisoning (Hill, 1950). They may be viewed as the result of a functional isolation of the cerebral cortex which is not yet or is no longer subjected to a subcortical (hypothalamic) control.

Perhaps it is permissible to add that neurophysiological investigations of the type reported in this paper cannot be expected to do more than to present an outline of the psychophysiological relationship. However, they explain at least in principle the qualitative and quantitative changes in sensations and perceptions which result from hypothalamic-cortical discharges under conditions of emotional excitement. Other and still more complex psychic events such as learning and memory which are undoubtedly cortical in origin are influenced by emotional processes. This is probably the cause of the greater retention for events experienced in youth than at later phases of life. In the light of Penfield and Rasmussen's (1950) Klüver and Bucy's (1938) observations, which link memory processes with the temporal lobes, these data may at least partially be interpreted as being due to a hypothalamic discharge which affects primarily the temporal lobe of the brain. The experiments of Adrian on attention and the animal experiments reported earlier provide the evidence for the assumption of a restricted activation of the cortex under the influence of hypothalamic discharges under certain conditions.

It is common experience that various types of emotion are accompanied by different forms of hypothalamic "downward" discharges. Depending on the personality and the kind of emotion involved parasympathetic or sympathetic discharges may predominate. Even the layman is familiar with the outward manifestations of these discharges in the face (pallor, flushing) and investigations on the variations of the blood sugar (Gellhorn, 1943, 1953*d*) and of the state of the motor and secretory activity of the gastro-intestinal tract (Wolf and Wolff, 1947) have furnished many examples for the variability of the autonomic discharge. The writer has suggested that the autonomic "downward" discharge from the hypothalamus as well as the "upward" discharge to the cerebral cortex varies widely in pattern in different forms of emotional drives. Mood and action (physical as well as mental) are intimately interrelated and every intel-

lectual worker knows only too well from his own experience that a certain task may be easy in one state of mind (i.e. mood) and impossible in another. In the light of the work presented in this paper this means that a rather specific type of hypothalamic-cortical discharge may facilitate certain complex cortical activities.

These ideas are appended with some trepidation. Science is identified in wide lay and professional circles with the accumulation of facts and any remark going beyond it is criticized as speculation or fancy. Perhaps the criticism of as outstanding a neurologist as Walshe that neurophysiology shows a too narrow technological spirit is worthy of consideration. In matters which like those discussed in the present paper are of human concern it may pay to listen to representatives of the humanities who question that Truth is solely determined by facts[1] and emphasize that "the truth of things depends in large part on the perspective in which one places them."[2]

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[1] "We have become so democratic in our habits of thought that we are convinced that Truth is determined through a plebiscite of facts" (E. Heller. "The Disinherited Mind." Cambridge, 1952).

[2] R. Callois. "Diogenes," 1:114, 1953.

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THE FUNCTION OF THE CEREBRAL CORTEX

BY

WILLIAM GOODDY AND MARGARET REINHOLD[1]

(From the National Hospital, Queen Square, London, W.C.1)

THERE is a general belief derived from clinical neurology and from the study of the physiology of the nervous system that the superiority of man, in movement and sensation, over other creatures, is due to his possession of cerebral hemispheres proportionately larger, heavier and containing more cells than those of any other species. From this belief, the assumption has been made that skilled movements, fine sensations, and even complex functions and cognitive behaviour are either "localized" or "represented" in the cortex. Thus Wright (1952) states, "Generally speaking, the body is represented upside down in the cortex."

Elaboration of the notion that movement, or even muscles, are represented in the motor cortex has given rise to the common belief (i) that skilled movements result from impulses originating in certain specific blocks of cortical tissue, (ii) that these blocks or areas may be microscopically determined from the study of particular cell patterns. For example, Penfield and Rasmussen (1950) state that areas 4, 3 and 17, cytoarchitectonically determined by Brodmann, may be considered as functional units, although others, similarly determined, may not.

Although there is a tendency to criticize the false precison of cortical maps (Gooddy, 1949; Denny-Brown, 1950; Gooddy and McKissock, 1951) the existence of "centres" and "areas" in the cortex "representing" other parts of the body in an unquestioned tenet of modern neurological thought and teaching. Functions are "localized" in these "areas" and "centres." The behaviour of the parts is also "represented." For example, Humphrey and Zangwill (1952) state: "The absence of primary agraphia in this case (unlike those previously reported) is ascribed to the patient's preference for the right hand in writing. It is suggested that, whereas the speech functions were represented in the right hemisphere, the central mechanisms governing writing had been organized on the left side." Clark (1948) states "If representation *on* the motor cortex is not of muscles and if representation is not punctate, there is left only multiple

[1] Holder of a Research Grant from St. George's Hospital.

movement representation." For an example from neurology, Jackson (1887) said: "The central nervous system . . . consists of three levels, lowest, middle and highest; these, respectively, represent, re-represent, and re-re-represent all parts of the body." We see here the use of the word "representation" by psychologists, a physiologist and a clinical neurologist, in three quotations taken from a large collection. We know that great arguments take place as to whether structures or functions, muscles or movements, are represented or localized. We never find, however, that any discussion takes place regarding the use or meaning of the word "representation." In many works, such as, for example, Sherrington's "Integrative Action of the Nervous System," Penfield and Rasmussen's (1950) "The Cerebral Cortex of Man," and Hughlings Jackson's "Selected Writings," the word is extensively used without any suggestion as to its meaning. In a search for a definition we have not found any save those which fall back on experimental procedure. Thus Brain (1951) states "Since the electrical excitation of different parts of the precentral convolution evokes movements of different parts of the body, we are justified in speaking of the representation of parts of the body in this part of the brain." Yet it is to the actions and feelings of the intact and normal person that the notion of representation is supposed to apply; for the experimenter does not claim (although logically he should do so) that representation of movements or parts of the body exists in damaged or excised parts of the brain.

In this paper we wish to suggest that parts of the body, voluntary movements, sensations, cognitive behaviour and ideas are not "localized" or "represented" in the brain.

Nothing resides in a nerve cell but the chemical constituents, physically disposed. In nervous tissue there are no ideas or sights or sounds or movements. Above all, there are no models, images or "little men." Nervous tissue does no more than transmit nerve impulses. During life we can suppose there is a vast number of ceaselessly travelling impulses in the brain. By means of experimental procedures, we may observe the results of the passage of an impulse in nervous tissue. We may also introduce, artificially, a new impulse. We call this "stimulation." Such a procedure may result in movement of a distant part of the body. It may also result in the experiencing of a sensation whether applied to the cortex or to a peripheral nerve.

We are not, however, able to observe more than this. Because a part of the body moves in response to cortical stimulation, that part is said to be "represented" in the area of the cortex stimulated. The same part which moves in response to stimulation of the peripheral nerve is not

said to be represented at the point on the nerve where the stimulus is applied. In either case we are able to observe only the physical results of experimental procedure, and there is no logical reason for allocating representation to one and not the other.

Consideration of Recent Experimental Evidence Relevant to "Representation"

Of recent years, Penfield in Canada and Carmichael in London, and their associates, have been accumulating data from experimental cortical stimulation in the human subject. The most important conclusions which we draw from their work are:

(i) that cortical stimulation never results in such movements as are seen in daily human use. The following three quotations are taken from Penfield and Rasmussen (1950) "Cerebral Cortex of Man." "The movements produced by cortical stimulation are never skilled, acquired movements but instead consist of either flexion or extension of one or more joints, movements which are not more complicated than those the newborn infant is able to perform" (p. 47). Stimulation produces vocalization but not speech (p. 88). "Such vocalization is a vowel sound, a cry without words. It resembles the cry of an infant... It also resembles the cry of some epileptics at the onset of a seizure" (p. 89).

(ii) As Bates (1953) has shown, movements of all four limbs occur after removal of a cerebral hemisphere, when the remaining hemisphere is stimulated. Possible reasons for the power still to move were suggested by Gooddy and McKissock (1951). Carmichael (1954), in a lecture (as yet unpublished) to the British Post-graduate Medical Federation, made clear the useful and purposeful behaviour of infants with absent or useless cerebral hemispheres.

It is therefore clear that it is not essential to have a cerebral cortex for the performance of those movements necessary for survival. Movements occur before the cerebral cortex is myelinated and even if the hemispheres of the brain are grossly deficient or absent. As life proceeds, the brain is trained (Gooddy and McKissock, 1951). This training, which is, fundamentally, the acquisition of use and understanding of symbols, results in superior powers. But the acquisition of such powers carries with it a greater possibility of disability if the brain is affected by disease. The untrained child can suffer severe damage to the brain with little in the way of symptoms, but the adult, fully trained, may be disastrously afflicted in similar circumstances of damage in the same region. If movements and sensations were represented in the brain it should follow that damage at a specific place in the brain at any age should result in the same defects.

Such standard defects are clearly not found. We must, therefore, seek to provide a more satisfactory theory of cortical function.

The following hypothesis of cortical function is now proposed:

The whole cortex (including those parts at present labelled frontal, rolandic, parietal, temporal and occipital) has no other function but to select, abstract, differentiate, integrate and condense rhythms or patterns of neuronal activity.

By so doing, the cortex enables a man to perceive sensations in a complex manner, to perform skilled movements, to use and understand systems of specific symbols such as language, to remember past experiences and to achieve conceptual thinking.

Certain blocks of the cortex are discovered to be the direct channels transmitting impulses concerned with the eventual recognition of specific sensations. For example, the occipital cortex transmits visual patterns, the temporal auditory patterns. Such differentiation may be acquired by use or training. Nevertheless, whether the patterns are in channels from eye or ear or skin or any other primary stimulus detector, all that the cortex does is to provide a mechanism for abstracting and integrating them.

We now wish to consider the hypothesis in more detail. The perception of sensation (and therefore the performance of voluntary movement) depends upon both physiological and psychological processes. Sensory stimuli, the transmission of which may be detected by *quantitative* methods, are perceived as sensations, which are *qualitative* experiences belonging to mental phenomena. It is not known during what stage of nervous activity sensory stimuli become perceived. It is known, however, that they may be perceived without the presence of the cortex (Carmichael, 1954, in lecture above mentioned).

Qualitative phenomena, which have no intrinsic temporal or spatial properties, are clearly related to *quantitative* phenomena, which can be metrically expressed by symbols representing space and time.

We suggest that the cortex, exercising its function as above outlined, is necessary for a variety of mental performances. These performances include the *judgment of sensory relationships*, upon which skilled movement and the experience of refined sensation depend: *memory*: the *learning, understanding and expression of symbols*, such as language, mathematics, and music (and also symbols of a personal non-specific nature); and *abstract thinking*, which gives rise to creative work in the form of concepts or works of art.

In a previous paper (Gooddy and Reinhold, 1953) we stated that sensory stimuli are received, transmitted and integrated in the nervous system as patterns of motion. We also attempted to show that all sensa-

tions, though objectively unmeasurable, are endowed by the perceiving individual with spatial, temporal and directional qualities. All sensations are perceived in perceived space, either within, upon, or in the area surrounding the body. They are also perceived in time, according to their serial relation to preceding and succeeding sensations. Sensations are dynamic and are also perceived as travelling from one point to another point, in relation to known areas on or within the individual's body and personal space. It is suggested that the spatial, temporal and directional properties of sensations are attributed to them by means of the active judgment (conscious or unconscious) of sensory relations. The judgment of sensory relationships is a *mental performance, and may be dependent upon the abstraction and selection of dynamic patterns of cerebral activity on the part of the cortex.* We now wish to show that fine sensations and skilled movements are dependent upon the attribution of spatial and other properties to crude sensations.

(1) Touch: In order to locate a single touch upon any part of his body, an individual must know his position in space, and the relation of the area stimulated to the rest of his body. He must know his right side from his left side, front from back, head from feet. Thus even a single uncomplicated sensation involves a number of patterns of cerebral activity, and an *active judgment* of sensory information must take place. In the case of three-dimensional feeling ("stereognosis") an individual must recognize size, shape, texture and nature of an object by touch, pressure and postural sensibility. He must understand the relative position and directional flow of one plane of the object to another, the whole being mentally integrated in a dynamic equilibrium. The sensations which he experiences as the result of the exploration of his moving fingers must also be related to past experience. The cortex selects, abstracts and integrates motion patterns of cerebral activity (which occur following the reception and transmission of sensory stimuli). The individual, having been presented with precise information, attributes, by means of mental activity involving the judgment of sensory relationships, the spatial and other characteristics to the sensations which are evoked. When these characteristics are established, *recognition* of the object may occur.

Appreciation of postural sensation requires the comparison and contrast of sensory relationships in the same manner.

(2) Skilled movements require similar precise sensory knowledge (Gooddy, 1949). Skilled movements are in fact performed solely by means of the voluntary alteration of multiple sensory relationships.

(3) Vision: Normal visual perception involves not only pure visual sensation but also sensations of other categories together with spontaneous

mental performance. We see objects as two and three dimensional patterns against, and distinct from, a background of other objects. We learn to see by means of experiment with and experience in space. The experience is partly visual, partly kinetic and tactile. In order to see objects in their correct location and orientation to gravity, we must be aware of our own orientation to gravity and compare objects with the position of our own bodies in space. The planes of objects vary in their appearance according to their distance from us and the angle at which they deviate from imaginary vertical and horizontal planes before us. As in the case of recognition by touch, recognition by vision requires the mental integration in a dynamic equilibrium, the total integration being related to our own bodies. Failure to achieve and maintain this complex performance results in disorientation of vision (Reinhold, 1954), one aspect of which is called "visual agnosia" by some writers.

It is suggested therefore that normal vision requires the ability to contrast and compare multiple sensory relationships, and that this ability is dependent upon the integrity of cortical function.

(4) Memory: Events and experiences of the past cannot be stored in the brain in the form of sensations contained in nerve cells. It is also unlikely that the act of remembering is a purely reflex association with a previously stored experience. Memory involves the act of recognition of an experience, when the latter recurs. This recognition is perhaps accomplished in the following manner. In infancy, a specific sensory stimulus causes cerebral motion patterns of a particular rhythm and rate. Sensory stimuli are, however, never isolated, and occur in association with others which produce their own patterns of cerebral activity. The specific sensory stimulus then occurs again at a later date together with a different set of associated sensory patterns.

The cortex is, however, able to select the common motion patterns of each sensory experience, integrate and perhaps condense them, to form some kind of new particular pattern. As a result of this selection and abstraction the child is able to recognize the pattern. The next time it occurs the recognition is an active mental performance.

(5) Symbols: It is precisely because the cortex functions as it does, abstracting, selecting and condensing cerebral motion patterns or rhythms to a basic unit or symbol that man has acquired the power to create and use symbols. Psychological behaviour may imitate physiological behaviour. The human cortex, because of its power of selection and abstraction, has provided the basis for the very high degree of symbolism which man is capable of using. The use of the symbols of language, mathematics, music, physics and so on are dependent upon cortical integrity. It must

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be remembered, however, that symbols can neither precisely nor completely express the reality of personal experience. Words give only inaccurate descriptions of sensations and feelings (which ultimate realities therefore can never be described in specific technical terms). The clinician notes the frequency with which patients at the onset of a disease are incapable of describing what exactly has been felt (especially when the lesion affects the cortex), for example in epilepsy or cerebral thrombosis. The symbol provides man with the concrete, which is apparently satisfying to him.

Individuals deprived by cortical lesions of the ability to express themselves in symbols may still be able to experience profound and complex emotions and sensations.

(6) Abstract Thinking: Abstract thinking is largely dependent upon symbols, which are dependent in turn upon the integrity of the cortex.

Clinical evidence.—In support of our hypothesis we wish to include the following clinical description. As mentioned above, Carmichael (1954) has demonstrated that unskilled movements can be performed and crude sensations experienced when the cortex has been removed, or, in the case of infants, when the cortex is congenitally absent. Skilled movements, however, and more subtle and complex sensations (described by Carmichael as "skilled" sensations) require the presence of an active cortex. We have stated above that we consider skilled movement and skilled sensation dependent upon the judgment of sensory relationships, which in turn depends upon the selection, abstraction and integration of sensory patterns by the cortex.

In clinical practice it is difficult to be certain that a cerebral lesion, whatever its nature, is confined to the cortex. The lesion may interfere with the blood supply of subcortical cells, or may cause pressure effects, or may produce œdema in deeper layers of the brain thereby altering their function.

The following patient suffered from cortical thrombophlebitis, and illustrates certain features probably caused by reduction or interference with cortical blood supply and œdema of cortical cells. His illness improved rapidly in a few days during treatment with antibiotics.

Case G. E. (under the care of Mr. Wylie McKissock), a right-handed man aged 36, an accountant by profession.

Six weeks before his admission to the Atkinson Morley Hospital, Wimbledon, the patient developed bilateral otitis media. He had had previous attacks of otitis media in 1940 and 1942, and during one of these the left ear drum had perforated spontaneously.

Five weeks before admission a right myringotomy was performed. His

left ear continued to discharge and two weeks before admission a left mastoidectomy was performed.

Two days before admission, the patient suddenly began to suffer from severe pain in the right side of his head. One day before admission his left arm became numb.

On admission the patient was drowsy and had a temperature of 100° F. There was slight neck stiffness. He had marked sensory disturbances in the left side of the body.

X-rays of the skull showed no abnormality, except for haziness of the mastoid aircells.

Ventriculography was immediately performed as the presence of a cerebral abcess was suspected. Only the right lateral ventricle was filled with air. This ventricle appeared normal in size, shape and position, and there was no evidence of a supratentorial expanding lesion of the right. A diagnosis of cortical thrombophlebitis was made and treatment was commenced with penicillin and streptomycin.

A day or two later the patient was alert and co-operative. His chief disability was a severe left-sided sensory disturbance resulting in what may be called a "sensory paralysis." Though power was extremely good on the left side, and the reflexes physiological, the patient had great difficulty in using the left arm and leg. He made violent, sweeping, clumsy movements with his arm. He broke a cup and a glass which he tried to hold in his left hand. He was unable to perform any of the routine tests for co-ordination without showing gross abnormalities. The patient did not know, without the aid of vision:

(i) the position of his left arm in relation to the rest of his body,

(ii) the position of the hand in relation to the arm,

(iii) the position of fingers in relation to the hand. He was unable to tell which of his fingers on the left hand was touched or grasped while his eyes were closed, although he felt the examiner's touch. He made guesses. For example, he said "That's my thumb," or "my forefinger" when his little finger was grasped. In the same way he was unable with closed eyes to localize any sensation on the left side, including his face and trunk, although he certainly perceived the sensation. He was, for example, asked to point with his right hand to the area to which a pin-prick was applied on the left side. When an area on the chest beneath the nipple was stimulated, the patient pointed—inconsistently—to an area above the nipple, or near the shoulder. Stimuli on the hand were localized in an inaccurate manner in the forearm. Pin-pricks applied to the forearm were localized either below their true site of origin, or above on

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the upper arm. The patient confessed he had great difficulty in knowing precisely where the pin had been applied. "I can feel it all right but I don't know quite where it is." The patient described the sensation as "spreading, not clear." Stimuli applied to the right side were always localized briskly and correctly, with particular accuracy when the right hand could be used to demonstrate the area stimulated, for example, on the face or chest. The patient was quite unable to tell the nature of an object placed in his left hand while his eyes were closed. He could feel the object, moved his fingers clumsily and ineffectually upon it, and could even describe it in some detail. For example, when given a nail file he could describe it as "hard, fairly long, cold, machine turned—" but he was quite unable to recognize it. The instant the object was placed in his right hand he was able to name it. When stimuli were applied simultaneously to the right and left sides the patient localized the sensation always to the right side only, apparently unaware of the left-sided stimulus.

When he was asked to take an object which was held before him with his *left hand* he made strong, almost compulsive movements to take it in his right hand. The right hand had to be forcibly restrained in order that he should take the object in his left grasp, which was wild and uncertain. Unless he moved swiftly with his left arm with sudden anxious precipitancy, he missed the object altogether. Being deprived of "skilled sensation," therefore, he was also unable to make skilled movements.

The patient showed, in addition, a tendency to neglect the left in copying designs and in drawing maps. On two occasions he omitted to draw the entire West Coast of England.

On one occasion he had some slight difficulty in recalling the topography of places very familiar to him, but this difficulty soon disappeared as his condition improved.

On discharge from hospital ten days after admission the patient was afebrile, alert and intelligent. He complained only of his left hand "which didn't feel quite normal."

The disabilities experienced by this patient illustrate our hypothesis. We suggest that the sensory patterns derived from his subcortical nervous structures were not subjected to analysis, elaboration and synthesis which normally occur in the cortex. Selection, abstraction, differentiation and integration of sensory patterns did not take place. The patient was therefore deprived of information by means of which he could make sensory judgments. He was aware of touch and pin-prick, but he could not localize these sensations on his body correctly. He knew that part of his hand was gripped but he was unable to say to which finger the stimulus was applied. He could determine the characteristics of a solid object

placed in his affected hand but he could not recognize it. The appreciation of "skilled" sensation and the performance of skilled movements are dependent upon the ability of the cortex to elaborate multiple sensory patterns and provide an infinity of sensory relationships.

We believe that this patient, suffering from disabilities now recognized as relatively common and amenable to investigation illustrates the simple principle which we have attempted to put forward. We have been careful to avoid neologisms involving the terms "gnosis" and "praxis" as we believe that such terms confuse the study of cortical derangements.

Conclusion

We may therefore conclude that the cortex behaves in much the same manner as the "mechanical brain," which should thus be more correctly described as the "mechanical cortex." The cortex selects, abstracts and integrates the motion patterns of cerebral activity. It is perhaps reasonable to assume that the more active the cortex in any one brain, the better will that brain resolve and integrate its activity, resulting in superior powers of judgment of sensory relationship, memory, symbol use and abstract thinking. The difference between the intellectual capacity of a "clever" man and a "dull" man, depends therefore not on relative *size* of their brains, but on the amount of activity of their brain. In this connexion, it is interesting to consider the stimulating effect of such drugs as caffeine and amphetamine which are said to increase cortical activity.

Finally we wish to emphasize that the cortex does no more than to abstract, select and integrate patterns of nervous activity. The cortex is not able to perform a judgment of any kind, nor initiate voluntary movement, nor see, nor hear, nor think. Only an individual may do these things. The cortex, however, provides the *basis* for the comparison of sensory relationships; for recognition, or memory; for symbols which with notions of space, time, direction and many other ideas, have enabled man to create calculating machines, symphonies and poems.

Our thanks are due to Mr. Wylie McKissock for permission to describe the patient under his care.

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THE PHYSIOLOGICAL MECHANISM OF REFERRED SHOULDER-TIP PAIN

BY

F. S. A. DORAN

AND

A. HALL RATCLIFFE

(*From the Department of Anatomy, Manchester University.*)

It is a well-known fact that irritation of the central part of the diaphragm, supplied by the phrenic nerve, produces pain over the insertion of the trapezius muscle into the posterior border of the lateral one-third of the clavicle and the medial margin of the acromion. This striking example of a "referred" pain interested John Hunter, and numerous attempts have been made, over the last one hundred and fifty years, to explain this phenomenon. The hypotheses fall into two groups, those postulating a mechanism sited in the spinal cord, which is the older, and those postulating a peripheral mechanism.

The hypotheses in the "central" group are all modifications and elaborations of John Hunter's. He explained this sensory delusion in the following way. The areas of the brain serving the shoulder and the diaphragm may, he thought, both be activated by either of the two afferents concerned; if they were, there must be a nervous connexion between them. Where the connexion lay he did not specify, but suggested that it might be within the central nervous system, and perhaps within the brain itself. Sturge (1883), however, localized the connexion to the spinal cord alone, and all subsequent writers in this group have followed his example, particularly Ross (1888) and Mackenzie (1909). Their idea was that the afferent impulses from deeply placed structures spread in the grey matter of the cord so as to involve the cells connected to the posterior root fibres supplying the superficial tissues of the body. These impulses from within the body were supposed to cause an "irritable focus" in the cord rendering it hypersensitive to stimuli normally "silent," arriving by the sensory nerves of the body surface. This version of Hunter's "nervous connexion" is accepted by several authorities. (Weiss and Davis, 1928; Morley, 1931; Capps and Coleman, 1932; Brodal, 1948.)

More recently the "central" explanation has been strengthened, clarified and restated by Hinsey and Phillips (1940), who suggest that afferent impulses from the deeper structures may lower the "threshold" in the spinal cord to afferent pain impulses from the body surface if they terminate on the "same group of neurones." If, as well as terminating in a "common pool" of neurones, the afferent impulses from the deep and superficial tissues are subject to the neurophysiological principles of "summation" and "inhibition," then the concept of an "irritable focus" in the cord may take on real meaning.

The alternative, or "peripheral," group of hypotheses is of more recent origin. It was suggested by Wernøe (1925) and by Penfield (1925), that "referred" pain was due to an autonomic reflex, originating in the deeper structures, which influenced the vessels in the skin. Following a similar line of thought Davis, Pollock and Stone (1932) put forward the idea that the alteration in the skin vessels "in some unknown way" produced a metabolite which stimulated the pain endings of the appropriate spinal cutaneous nerve. This idea has been advanced to explain "referred" shoulder-tip pain by Pollock and Davis (1935). On the basis of animal experiments Pollock and Davis concluded that afferent impulses pass up the phrenic nerve to the fourth cervical segment, then flow down the spinal cord to the upper thoracic area, whence they leave the cord through the anterior roots to join the sympathetic chain. Having reached the autonomic system they ascend to the stellate ganglion from which sympathetic fibres pass out to the skin of the shoulder where they enter a "sensory corpuscule" and set up a "physico-chemical" change which stimulates the somatic sensory fibres of the fourth cervical nerve, giving rise to shoulder-tip pain. It should be noted that a chemical irritant, produced peripherally, is regarded as an integral part of the physiological mechanism of pain by Lewis (1942).

Crucial Experiment

In order to test these two hypotheses the following crucial experiment was designed. In both the "central," and in the "peripheral" type of explanation the integrity of the terminal nerve-endings of the supraclavicular branches of the third and fourth cervical nerves in the skin of the shoulder area is essential.

A Crile's block dissection of the neck for the excision of secondary malignant glands removes all the supraclavicular cutaneous nerves arising from the cervical plexus. In a patient who has been subjected to this operation, stimulation of the phrenic nerve on that side of the neck should not cause shoulder-tip pain, because there are no cutaneous nerve-

endings to generate impulses from the body surface, or to be irritated by a chemical substance of sympathetic origin.

Therefore, a case of this type was chosen on which to perform the test. Fig. 1 shows the extent of the sensory loss in this patient.

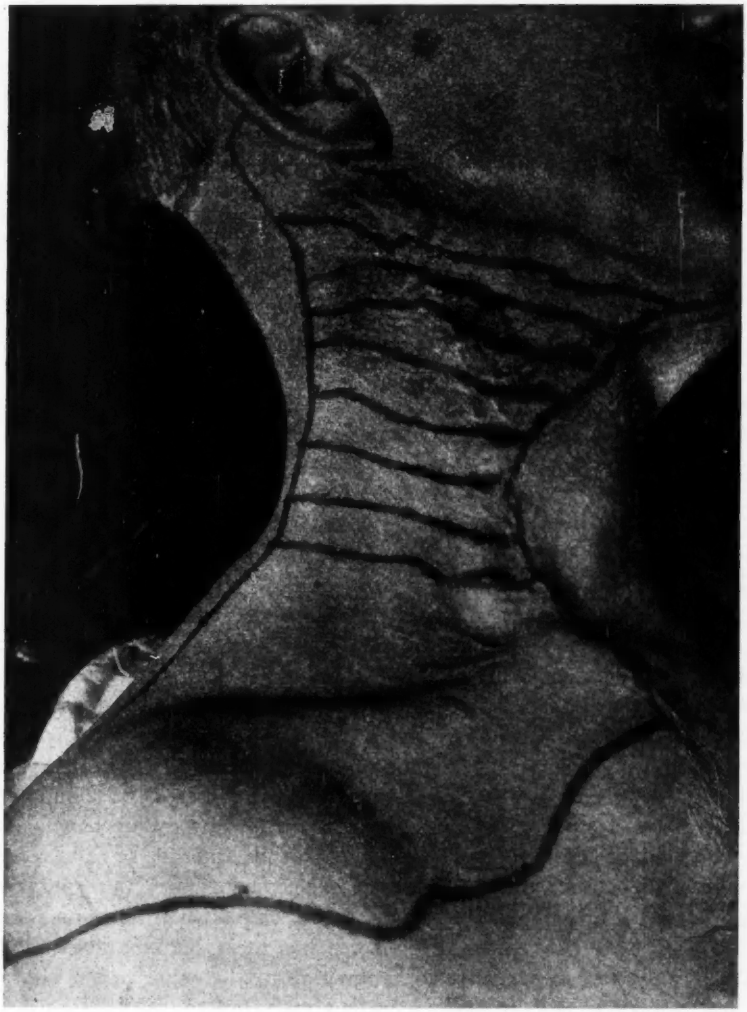

FIG. 1.—Photograph showing the extent of the anæsthesia, complete (unstriped) and incomplete (striped) in the patient upon whom the crucial test was performed.

Light touch was lost over the whole of the demarcated area; complete anæsthesia being confined to the territory of the supraclavicular branches.

The phrenic nerve was exposed; gently hooked up over a bi-polar electrode; and stimulated electrically. On every occasion the test was applied, sharp pain was felt by the patient in the anæsthetic "shoulder-tip" area.

The conclusions from these observations are obvious. First, that the autonomic nervous system plays no part in the production of "shoulder-tip" pain in man. Second, that a constant flow of sub-liminal impulses from the skin of the "shoulder-tip" area, to the "common pool" of neurones in the third and fourth cervical segments of the spinal cord, is not an essential part of the mechanism. It disposes, also, of any question of anti-dromic impulses in the supraclavicular nerves.

The Anatomical and Physiological Competence of the Phrenic Nerve with regard to Pain Production

From what has been said it follows that, in some way or another, the phrenic nerve is able to cause "shoulder-tip" pain. However, if the phrenic nerve were to possess certain anatomical and physiological properties it would require a less complicated explanation than otherwise.

Pain Fibres

Unlike other sensory modalities, pain has no specialized end-organs (Heinbecker and Bishop, 1935; Woollard, Weddell, Harpman, 1940), but the nerve fibres subserving pain are specific. Heinbecker and Bishop (1935) have shown that, irrespective of the frequency, or strength, of the stimulation, pain never arises from fibres subserving touch or pressure. Moreover it is fairly well established that pain impulses are conveyed by small myelinated fibres, $3\mu - 6\mu$ in diameter (Gasser, 1935; Heinbecker and Bishop, 1935), and that these fibres are less numerous in the afferent nerves from the deeper tissues, than in cutaneous nerves. It was necessary to discover, therefore, it the phrenic nerve possessed fibres of the appropriate size. Several phrenic nerves were removed, from post-mortem bodies, at the point where the nerve crosses the scalenus anterior, so as to correspond to the site of stimulation in the experiment. They were prepared and stained in the standard manner, and the size of their fibres measured on an enlarged photograph. One nerve was measured completed (1,762 fibres) and another partially. Examination of the other nerves showed considerable variation in their gross anatomy, but the size of the fibres was all of much the same range.

In the nerve which was examined completely the axon size was

estimated and recorded. The word estimate is used because, to a varying degree, the individual fibres become distorted in the process of fixation and cutting. Fig. 2 shows that the phrenic nerve possesses several hundred

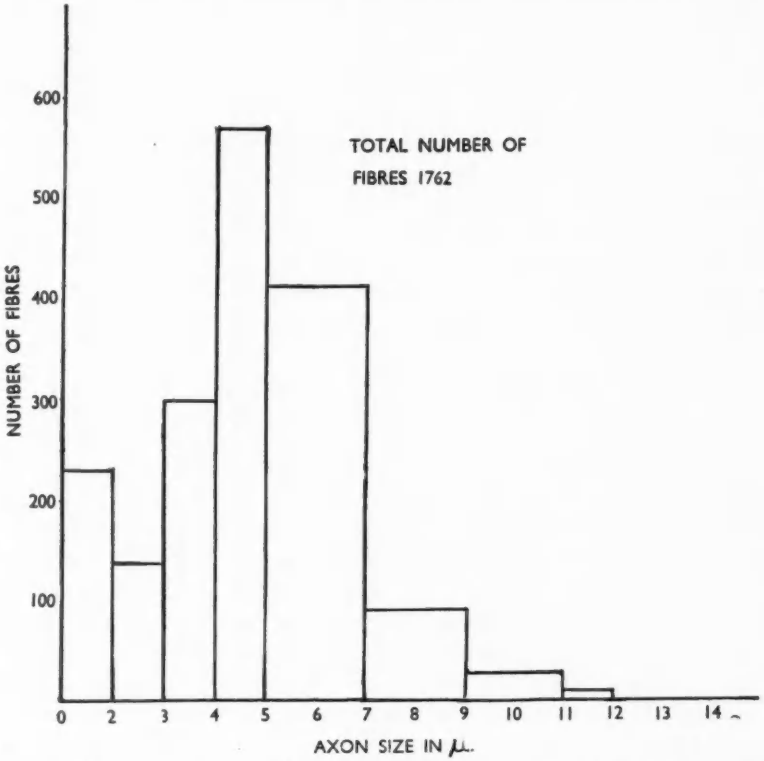

FIG. 2.—Diagram of the axon sizes in the phrenic nerve measured to the nearest μ.

fibres of the appropriate size for the transmission of pain impulses, the axon sizes ranging from $1\mu - 12\mu$.

Anatomically, therefore, the phrenic nerve can be accepted as competent with regard to the production of pain. The experimental test demonstrated that it was physiologically competent.

AN "IRRITABLE FOCUS" IN THE SPINAL CORD

The result of the crucial experiment was fatal to the "peripheral" autonomic hypothesis, but, although it demonstrated the capacity of the phrenic nerve to cause "shoulder-tip" pain without the help of impulses

from the skin of the shoulder, it did not prove that cutaneous impulses never play any part in the production of "shoulder-tip" pain.

It was shown by Morley (1931) that referred "shoulder-tip" pain initiated by artificially irritating the diaphragm, was abolished, or decreased in severity, by anæsthetizing the skin over the shoulder area with novocain. This suggests, strongly, that the afferent impulses from the skin do play a part. Moreover, there is the suggestion of Hinsey and Phillips (1940) that the summation of impulses passing up the phrenic nerve would have the effect of lowering the "threshold" in the spinal cord, thereby enabling cutaneous impulses to cross that "threshold," which they would not do otherwise. This idea rests on the assumption that the afferent impulses from the diaphragm and from the skin of the shoulder area, are delivered to the "same group of neurones" in the cord. To test this possibility the following experiment was conducted.

Experimental Test of "Summation"

In a series of patients undergoing a "phrenic crush" for the treatment of pulmonary tuberculosis, the phrenic nerve was stimulated, electrically, with the same apparatus that was used in the previous experiment. This apparatus, specially designed and made by one of us (A. H. R.) can deliver any type of stimulus desired, over a very wide range of frequencies.

In each case the phrenic nerve was stimulated until "shoulder-tip" pain was produced; the affected area of skin was then anæsthetized and the nerve was again stimulated. If "shoulder-tip" pain of phrenic origin was independent of impulses from the supraclavicular nerves, this procedure should have no effect. However, it was found that, after anæsthetizing the skin over the shoulder, cutting off the supply of impulses therefrom, a more powerful stimulus to the phrenic nerve was required to produce the pain.

It seems justifiable to conclude, therefore, that the afferent impulses from the phrenic nerve, and those from the supraclavicular branches of the cervical plexus, terminate in the same "common pool" of neurones in the third and fourth cervical segments of the spinal cord; and that "summation" occurs.

Evidently, the essential factor, in the experience of "shoulder-tip" pain is the "threshold" of the appropriate group of neurones in the spinal cord. Whether this "threshold" is crossed by impulses of diaphragmatic or cutaneous origin, or by a combination between them, is a matter of indifference for the brain.

The Irreversible Direction of Referred "Shoulder-Tip" Pain

Nothing which has been said, up to the moment, explains why the excitation of this particular group of neurones in the third and fourth segments of the spinal cord should produce sensation only in the "shoulder-tip" area. There is no logical reason why sensation should not be felt in the diaphragm itself. Questions of this kind prompted Lewis (1942) to reject the "central" hypothesis, because its hypothetical "irritable focus" in the cord did not explain why the reference is always to the superficial tissues, and never in the reverse direction. In spite of his rejection of the hypotheses, Lewis wondered if the phenomenon could be due to a very rich, and accurate, cortical representation of the skin, and a very meagre representation of the deeper tissues, so that, in consciousness, its call for attention was always drowned by the deafening clamour of the cutaneous impulses. Recent investigations into the cerebral background of consciousness (Adrian, 1947; Penfold and Rasmussen, 1950) leave no doubt that the exact nature and site of any particular experience depends entirely on which group of brain cells is activated. Probably, therefore, the explanation why the direction of reference in referred "shoulder-tip" pain is always to the superficial tissues, is because the diaphragm has no cerebral representation at all. In other words it can only attract attention to itself by "pulling somebody else's doorbell." This confirms the conclusion reached over twenty years ago by Woollard, Roberts and Carmichael, (1932) that the locality of a referred pain is due to the action of higher centres stimulated by the activity in the spinal segment corresponding to the peripheral nerve concerned.

Conclusions

(1) The autonomic system; producing vascular and metabolic changes in the skin of the "shoulder-tip" area plays no part in referred phrenic pain.

(2) Antidromic impulses in the supraclavicular branches of the cervical plexus play no part in the production of referred phrenic pain.

(3) Impulses from the diaphragm and from the "shoulder-tip" area terminate in a common group of spinal cord neurones.

(4) The neurophysiological phenomenon of "summation" occurs between the impulses originating in the phrenic nerve and those from the supraclavicular cutaneous nerves.

(5) The "summation" between these two sources is not essential to the production of referred "shoulder-tip" pain.

(6) Impulses of phrenic origin alone can cross the "threshold" of the

common group of neurones in the spinal cord, leading to "shoulder-tip" pain, without any assistance from the cutaneous branches of the third and fourth cervical segments.

(7) Pain is always felt in the "shoulder-tip" area because only the superficial tissues have distinct cerebral representation; the diaphragm, having none, cannot reach consciousness as an independent entity.

We wish to thank Professor John Morley for his critical scrutiny of our work and its conclusions. Also, we wish to thank Professor G. A. G. Mitchell for his help and guidance in our study of the fibres in the phrenic nerve. We are indebted to Mr. Pearson for preparing the sections of the phrenic nerve, and to Mr. Howarth for the photographs from with the measurements were made.

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TUBERCLE BACILLUS FRACTIONS IN EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS

BY

J. COLOVER[1]

(From the Canadian Red Cross Memorial Hospital, Taplow, Bucks)

FOLLOWING the work of Rivers and Schwentker (1935), it was discovered by Morgan (1947), and Kabat, Wolf and Bezer (1947), that an encephalomyelitis could be produced in monkeys by the intramuscular injection of homologous brain mixed with the Freund adjuvants, namely heat-killed tubercle bacilli suspended in paraffin oil with an absorption base (Freund and McDermott, 1942). Since an acid-fast bacillus is an essential ingredient, the components of these bacilli may bear a special relationship to those of the central nervous system of certain mammals. Knowledge of the nature of the substance or substances in the bacilli responsible for the production of the encephalomyelitis might therefore help the understanding of this reaction and lead to the development of more direct methods of investigation.

This work was therefore undertaken in order to isolate and identify as far as possible the active ingredient of the tubercle bacillus. Fractions were obtained from tubercle bacilli by the use of various solvents and by digestion processes, and their capacity to produce encephalomyelitis tested.

Much information has been derived from previous attempts to isolate biologically active fractions of various kinds from the tubercle bacillus. Sabin, Doan and Forkner (1930) and Anderson (1929) have worked on the lipid fractions and isolated a fatty acid which was called phtioic acid.

In this country Polgar and Robinson (1943, 1945) and Polgar (1948) have worked on the long-chain fatty acids present in the phosphatide fraction and the biological activity of various natural and synthetic fatty acids have been investigated by Ungar, Coulthard and Dickinson (1948). Areas of necrosis and granulomatous and giant-celled reactions have been produced with these substances after intraperitoneal injection. Raffel (1948) and Myrvik and Weiser (1952) have found biological activity

[1] Assisted by a grant from the Medical Research Council.

present in a wax-tuberculoprotein fraction, soluble in chloroform, which was capable of converting a tuberculin-negative animal into a tuberculin-positive one, although the latter workers found it necessary to use as much as 50 mg. of material per animal. Polysaccharide material has been isolated by Heidelberger and Menzel (1934, 1937) and Haworth, Kent and Stacey (1948). The latter found that the somatic polysaccharide had antigenic properties. Choucroun (1947) by means of paraffin-oil extracts of killed tubercle bacilli was able to isolate two biologically active agents, one a protein component, and the other a chloroform soluble carbohydrate-lipid complex. The latter substance had a remarkable capacity to produce pulmonary lesions.

The results obtained in the experiments reported in this paper show that the non-lipid part of the human tubercle bacillus contains an ingredient which is essential for the production of allergic encephalomyelitis in guinea-pigs, and that the extracted lipid fractions do not by themselves have this effect, although it is too early yet to state whether or not they possess any modifying influence.

Apart from endeavours to elucidate the mechanisms involved by interpreting the histological appearances, attempts to advance knowledge about the reaction have followed two main lines. One has been to investigate the nature of the agent present in the brain emulsion used, and it would appear that the substance is a lipoprotein or proteolipid, Olitsky and Tal (1952) Goldstein, Kolb, Mason, Sayre and Karlson (1953); the other has been to investigate the problem from the immunological aspects, Thomas, Patterson and Smithwick (1950), Lumsden, Kabat, Wolf and Bezer (1950). The line of attack on the problem described here provides yet another method of investigation which it is hoped may link up with the other methods already mentioned.

Methods and Materials

Various fractions have been obtained by extraction or digestion processes from a mixture of three strains of heat-killed human tubercle bacilli, used singly or in combination as a substitute for the whole bacillus.

Preparation of Extracts and Fractions from Tubercle Bacilli

The fractions and extracts mentioned in Tables I and II were prepared as follows:

A. Lipid solvents.—Bacteria used for the extractions were human tubercle bacilli, a mixture of three strains, and heat-killed in an autoclave. They had been grown on a synthetic medium and were obtained from the Ministry of Agriculture and Fisheries, Weybridge. They were subjected to extraction with acetone in a Sohxlet apparatus for two days. This crude extract is designated the acetone-soluble fraction. The residue was then similarly extracted with isopropyl ether for a further two days and yielded the isopropyl-ether-soluble fraction, which is waxy in nature.

The acetone-soluble fraction contains mainly phospholipids. The residue left after these two extractions is referred to as Residue 1 in the tables. It was obtained from Messrs. Glaxo Laboratories Ltd. This Residue 1 material represents about 90 per cent of the dry weight of the bacillus. It was further treated in two ways as follows: One part was extracted in the cold by shaking for twenty hours at room temperature with a mixture of chloroform and methanol in the proportions of 2/1 v/v using 500 ml. of solvent to 10 grammes of residue. The material which went into solution formed the so-called lipoprotein fraction. It was dried by evaporation under reduced pressure before use. The insoluble residue from this extraction was then further extracted both with chloroform and a chloroform methanol mixture in a Sohxlet and a reflux apparatus for eleven days altogether. The residue left is labelled Residue 2 in the tables. The other method of extraction of Residue 1 was in a Sohxlet apparatus with a 2/1 v/v mixture of chloroform and methanol continuously for seven weeks. The solvents were changed after the first forty-eight hours and then at weekly intervals. At the end of 7 weeks traces of so-called lipoprotein were still coming out but the amounts were too small to measure accurately. The amount of Residue 1 used was about 4·5 grammes and it lost about 11 per cent of its weight in this extraction. The insoluble material left was labelled Residue 3 in the tables. It represents about 80 per cent of the whole dry bacillus and is no longer acid-fast by the Ziehl-Neelsen staining technique. The lipoprotein which passed into solution was then suspended in Bayol F without further concentration and the solvents were evaporated at about 50° C. under reduced pressure. A clear solution was obtained when 40 ml. of Bayol F were allowed for every 50 mg. of lipoprotein.

B. Digestion processes.—(1) Residue 1 was digested with concentrated hydrochloric acid for 24 hours at 37° C. and the residue tested for activity.

(2) Papain digestion. Residue 1 was digested with papain for two days at 37° C. followed by one hour at 60° C. The supernatant was then poured off and fresh papain was added and digestion allowed to proceed for a further two days at 37° C. The amount of Residue 1 used was 450 mg. and the yield of undigested material obtained was 266 mg. The amount of papain used for each digestion was 50 mg. This residue was also tested for activity.

C. Other products.—Purified Protein Derivative obtained from the Ministry of Agriculture and Fisheries, Weybridge, was also tested for activity.

The animals used have been guinea-pigs, either white or albino from a stock known to react well to the lipoid fractions made from the tubercle bacillus. They were quarantined for one month before use. A number were tested for tuberculin sensitivity and were found to be tuberculin-negative, but animals so tested were not used for any work in which the encephalomyelitis was induced. All were healthy animals and during the experiments they were kept in cages in groups of two or three. They were fed on the standard laboratory diet of hay, oats, bran and cabbage. Male and female animals were used, weighting between 300 and 600 grammes. They were injected intramuscularly on four occasions at weekly intervals, unless stated otherwise, and killed on or about the thirty-first day of the experiment. Some were killed earlier because they were so severely affected that they were not expected to live overnight. At first groups of 10 animals were used for each trial, but later fewer were used in view of the high percentage of positive results obtained with active fractions. Animals which did not survive ten days were excluded from the results because it was too soon for allergic encephalitis to develop.

The site of injection was into the paravertebral muscles of the back, just medial to the scapular border. Each injection consisted of 1 ml. of an emulsion containing 0·4 ml. of a 12·5 per cent homologous brain suspension in 1 per cent carbol saline,

XUM

0·2 ml. Falba[1] and 0·4 ml. Bayol F[2] in which was suspended the tubercle fraction under investigation or the whole bacillus.

The brains used for the emulsion were removed under sterile conditions from animals which had been bled out under anæsthesia. After checking for sterility they were homogenized in a N.I.R.D. tissue homogenizer with carbol saline and the resulting homogenate was heated in a water bath for 45 minutes at 60° C. The material was made up in bulk and each batch was confirmed for activity by a trial with the whole bacillus. A portion from each batch of brain homogenate was used as a control injection material, suitably combined with Bayol F and Falba. All the emulsions were repeatedly checked for sterility each time they were used and no contamination was found. Attempts to grow organisms from the brains of paralysed animals both by aerobic and anaerobic culture was not successful. In one series attempts were made unsuccessfully to transfer the paralysis by intracerebral injection of saline suspensions made from the brains of paralysed animals to normal animals.

About the 31st day of the experiment the surviving animals were bled out under chloroform anæsthesia and then the brain and spinal cord completely exposed and fixed in situ in 10 per cent. formol saline. A full post-mortem was performed on each animal. Later after fixation, the brain and spinal cord were dissected out and embedded either in paraffin or paraffin and celloidin. Paraffin or doubly-embedded sections were usually stained by the following techniques: Ehrlich's acid hæmatoxylin and eosin, Weigert's iron hæmatoxylin and van Gieson's mixture, Nissl's stain, Loyez method for myelin, and Lendrum's phloxine-tartrazine. Frozen sections were also made and stained with Ehrlich's hæmatoxylin and Scharlach R. In one positive series the lungs were examined fresh under a dark ground illumination for evidence of fat embolism—no such evidence was found. Portions from various organs and from the injection sites were embedded in paraffin and examined histologically.

Results

The results obtained with the various fractions prepared above are enumerated in Table I.

Animals developing encephalomyelitis showed tremors of the head, jerky movements, paralysis of the limbs, especially the hind-limbs, swaying gait, flaccidity and weakness of the spinal musculature and nystagmus. Some showed convulsive movements usually just before death. Generalized symptoms such as loss of weight, sluggish movements and particularly loss of the righting reflexes were often noted preceding the onset of frank paralysis. Marked local intramuscular lesions in the form of nodules at the injection sites were frequently observed, their size and outline often were accentuated by the generalized wasting.

[1] Falba. A lanoline-like substance obtained from Messrs. Pfaltz and Bauer Inc. New York, U.S.A.

[2] Bayol F. A paraffin oil made by the Esso Standard Oil Co., New Jersey, U.S.A.

Notes.—(*See opposite.*) (*a*) Experiment 1-5 was allowed to run for 43 days. All the other experiments were terminated on the 31st day.

(*b*) Experiment 3–7. More exhaustive attempts with the fraction used in this experiment failed to produce the encephalomyelitis.

TABLE I.

No. of expt.	Fraction with brain suspension	Dose of fraction per ml.	Total No. of injections	No. of guinea-pigs	No. surviving 10 days	No. surviving 30 days	Onset of paralysis 11–14	Onset of paralysis 15–19	Onset of paralysis 20–24	Onset of paralysis 25–30	Ratio No. of paralysed animals to No. surviving 10 days	Ratio No. of animals showing encephalomyelitis to No. examined histologically
1–5	Whole bacillus strain 666	2 mg.	4	9	9	4	)	2	0	2	6/9	8/9
1–5 Control	Nil	Nil	4	6	6	6	0	0	0	0	0/6	0/6
1–10	Acetone soluble fraction	0·5 mg.	4	12	9	8	0	0	0	0	0/9	0/6
3–7	Isopropyl ether soluble fraction	0·5 mg.	3	6	6	6	0	0	0	0	0/6	0/6
1–6	Residue 1	5 mg.	4	10	10	2	0	7	2	0	9/10	5/5
1–6 Control	Nil	Nil	4	5	5	4	0	0	0	0	0/5	0/5
1–7	Residue 1	0·5 mg.	4	10	10	1	1	1	7	1	10/10	9/10
1–7 Control	Nil	Nil	4	5	5	5	0	0	0	0	0/5	0/5
1–8	Residue 1 Brain emulsion omitted	5 mg.	4	8	8	7	0	0	0	0	0/8	0/7
2–1	P.P.D. protein	0·5 mg.	4	10	9	8	0	0	0	0	0/9	0/6
2–2	Residue 1 after treatment with papain (residue left)	1 mg.	1	12	7	1	3 died	1	1	0	2/7 and 3 deaths	2/2
3–0	Total cold extracted lipoprotein (20 hours)	0·78 mg.	4	5	5	5	0	0	0	0	0/5	0/5
2–9	Residue 2	0·5 mg.	4	10	7	3	1	1	3	0	5/7	5/7+1 extensive hæmorrhages in C.N.S.
3–3	Residue 3 7 weeks Sohxlet residue	0·5 mg.	4	8	8	5	2 died	1 died	1	4	5/8 and 3 deaths	6/6
3–4	Total undried lipoprotein 7 weeks extractions Sohxlet	0·5 mg.	4	8	8	8	0	0	0	0	0/8	0/5
3–1	Residue after hydrochloric acid digestion	0·5 mg.	4	6	6	6	0	0	0	0	0/6	0/6

Neurological signs and lesions in the central nervous system obtained with 2 mg. of strain 666 heat killed human tubercle bacilli per ml. of emulsion (Series 1–5).—This experiment was allowed to run for forty-three days. The signs and lesions which developed in the central nervous system followed the usual pattern. 8 animals out of 9 developed the lesions of allergic encephalomyelitis. Typical granulomatous reactions occurred in the walls of the small vessels of the brain and spinal cord and localized patches of meningitis were seen. Narrow zones of demyelination occurred perivascularly, mainly in the corpus callosum and fornix. There were areas of perivascular proliferation of microglia and also in some places subpial proliferation of microglia. One animal showed shrinkage of the oligodendroglia. No changes were observed in the nerve cells.

Neurological signs and lesions in the central nervous system obtained with Residue I (Series 1–6, and 1–7).—As can be seen from Table I this material was very active indeed in producing paralysis and neurological lesions. It was used in two strengths 5 mg. and 0·5 mg. per ml. of emulsion. In the intracerebral venule walls gross granulomatous proliferation occurred. Large granulomata also occurred in the tela chorioidea dorsal to the third ventricle which tended to infiltrate into the commissural white matter above. Areas of demyelination were very commonly seen especially in the corpus callosum. Severe meningeal reactions were also observed. The reactions in this group of animals were more extensive than those of any other series and more than those seen with the whole tubercle bacilli.

The intracerebral vessels were greatly increased in number and both capillaries and larger vessels were congested. The venules were very prominent owing to their thickened walls and the surrounding proliferations of microglia (figs. 1 and 2). In paraffin section 5 μ thick, up to twelve cells radially could be counted in the thickness of the vein walls. Cells with oval, curved or irregularly shaped nuclei formed the main body of this cellular proliferation, with occasional polymorphonuclear leucocytes. The endothelial lining was intact and there was no evidence of thrombosis. At the base of the brain the meninges were heavily infiltrated by small round and histiocytic cells with occasional polymorphonuclear leucocytes (figs. 3 and 4). These meningeal reactions were especially conspicuous around the dilated blood vessels and in the folds of the leptomeninges. The meningeal fold at the level of the diencephalon showed gross granulomatous thickening (fig. 5) especially in relation to the vessels and this band of granulomatous tissue tended to reach dorsally to the peduncular region towards the zone of attachment of the chorioid plexus of the third ventricle. Dorsal to the third ventricle severe reactions were seen in the superior tela chorioidea (fig. 6) which tended to spread into the white matter

above and laterally. In these granulomata in the superior tela chorioidea the following cell types could be identified:

(1) Cells with large pale oval nuclei (hæmatoxylin and eosin) with a loose reticulum of chromatin, sometimes with vacuolated cytoplasm which had a polygonal outline (fig. 7).

(2) Numerous short thick rod-shaped forms, frequently curved, flask shaped or kidney shaped (fig. 8).

(3) Elongated narrow rod cells (fig. 9). Transitional cells between the two latter forms could also be observed (fig. 9).

(4) Cells with densely basophilic round nuclei with the chromatin material arranged peripherally in clumps and similar nuclei showing a dense nucleolus. These cells were considered to be of the lymphocytic series.

(5) Cells in mitotic division.

(6) Polymorphonuclear leucocytes.

The ependyma was intact.

In addition to these granulomatous changes, areas of demyelination were very frequent, especially in the corpus callosum (fig. 10). They were usually perivascular around small veins, but occasionally they were diffuse or even periventricular. The latter, however, were infrequent. In some animals the areas of perivascular demyelination tended to coalesce to form larger areas. In such larger areas profuse microglial reactions might be seen. Generally the borders of the demyelinated areas gradually faded off into the normal tissues. In some of the demyelinated areas little was seen in the way of cellular reactions either in the white matter or in the adjacent vessel walls. In some animals there were areas of extravasation of blood bordering the demyelinated areas. Around many vessels in the brain substance was a considerable proliferation of the microglial cells. Sometimes they would be arranged concentrically, but sometimes especially in demyelinated or necrotic areas irregularly. Both rod-shaped and amœboid forms were frequent.

The brain-stem, cerebellum and spinal cord were similarly involved, but tended to be damaged less often than the larger commissures of the brain. Very little parenchymatous change as distinct from vascular changes was seen in the spinal cord. In the pons and medulla focal collections of pericapillary microglial tended to predominate. Microglial reactions in the cord tended to be situated in the anterior horns. No changes of note were found in the neurones apart from some hyperchromatic staining and shrinkage of the cell bodies in the Purkinje cells of the cerebellum seen in the Nissl-stained sections only very occasionally.

Neurological signs and lesions in the central nervous system obtained

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with Residue 3 (Series 3–3).—This was used at the dose strength of 0·5 mg. per ml. of emulsion.

This material was less active than Residue 1 but in some respects seemed to be more active than the whole tubercle bacillus. Out of 8 animals, 3 died and 5 showed paralysis, which was quite severe. Five animals out of the 8 were still alive on the 31st day of the experiment as against 1 out of 10 with Residue 1.

Cellular reactions in these animals were almost as profuse as in the previous series and seemed to be of the same type. The amount of perivascular demyelination, however, appeared less. Similar reactions were seen in the tela choroidea superioris (fig. 11) spreading into the body of the fornix. Also granulomatous reactions tended to occur at the site of attachment of the choroid plexus of the 3rd ventricle (fig. 11). The vessel wall changes were very well marked (figs. 12 and 13). Perivascular demyelination still occurred but was much less on the whole (figs. 15 and 16). Some astrocytic proliferation was present around the vessels involved but it tended to be masked by the microglial proliferation. Involvement of the spinal cord vessels in this group of animals seemed to occur more often, but this may have been fortuitous, although it should be remembered that the survival rate in this group was higher than in the previous group and so histological differences might in part have been due to the longer time for the lesion to develop rather than to chemical differences between the fractions used.

Lesions in other groups of animals.—Rather surprisingly the treatment of Residue 1 with papain did not destroy its activity and the lesions of two animals in this group showed all the histological features including the perivascular demyelination although these animals had only one injection each. It was rather unfortunate that most of the animals in this series died very early in the experiment.

TABLE II.—ALLERGIC ENCEPHALOMYELITIS—TUBERCLE BACILLUS FRACTIONS

Fraction	*Result*
Acetone soluble. Sohxlet extraction for 2 days	−ve
Isopropyl ether soluble. Sohxlet extraction for 2 days	−ve
Residue 1 (i.e. after acetone and isopropyl ether extraction) ...	+ve
(*a*) Cold extracted methanol/chloroform 1 day	
Extract	−ve
Residue 2	+ve
(*b*) Sohxlet extraction methanol/chloroform 7 weeks	
Extract, undried	−ve
Residue 3	+ve
(*c*) Papain treated Residue 1	+ve
Purified protein derivative	−ve

In the group marked negative in Table II, which summarizes the results, a few animals showed occasional minute hæmorrhages in the grey matter of the spinal cord. Only one showed any symptoms. Otherwise these negative groups did not show any changes in the central nervous system. A fraction was regarded as inactive when no animal in which that fraction was used in place of the tubercle bacillus developed encephalomyelitis.

Discussion

These results indicate that an ingredient essential to the production of allergic encephalomyelitis in guinea-pigs is contained in the non-lipoid fraction of the tubercle bacillus, and that this substance resists treatment with boiling fat solvents for long periods.

The acetone-soluble and isopropyl-ether-soluble fractions do not produce any reaction in the central nervous system when used in dose ranges which are adequate for the active fractions. If one compares the activity of the active residues Residue 1 and Residue 3 with each other and with the whole tubercle bacillus, then the most active seems to be the Residue 1 material, closely followed by the Residue 3, whilst the least active is the whole bacillus. However, one cannot definitely exclude the possibility that the particular batch of bacilli used for the extraction may have been more potent than the single strain used as the whole bacillus. It is, however, possible that the initial extraction processes have indeed increased the activity of the material by removing some lipid matter and so liberating the active biological groupings necessary for this reaction. The so-called lipoprotein fraction alone does not produce the reaction but in view of the somewhat diminished activity of the material after its extraction, one cannot completely, at this stage, exclude it from participation in a subsidiary role. It is possible, however, that the prolonged extraction over seven weeks with the boiling chloroform methanol may have affected the active non-lipid moiety in an unfavourable way. The active Residue 3 material may still contain clumps of unextracted lipid, but apart from such small amounts, it is now fairly free of lipids. A rather unexpected finding is that the Residue 1 is still active after digestion with papain and we hope to subject this material to further processing. The active material is largely made up of polysaccharide and proteins and it is most probable that the activity is related to these, although it is still conceivable that the active moiety belongs to neither class of substance. However, this latter possibility is regarded as improbable.

It is not yet proved that this reaction is due to an immunological process, but these experiments may be considered to provide support for

this view. If the reaction producing experimental allergic encephalomyelitis is an immunological one, it would seem that the antigen is composed of two parts, one contained in the non-lipid part of the tubercle bacillus and the other part, probably a hapten, in the proteolipid substance of the brain tissue, as described by Olitsky and Tal (1952). It is easy to visualize how the brain proteolipids might replace the tubercle bacillus lipids and thus form a complete antigen, in a manner analogous to that used by Morgan (1943), who made blood group A substance antigenic by combination with the protein component of the O antigen of *Shigella shigæ* to form a complex which was a complete antigen. Such a union presumably would occur intracellularly in the granulomata at the injection sites and would account for the necessity for the two factors to be injected at the same site. The presence of this antigenic material in the tissues might lead to the development of intracellular antibodies which cause the encephalomyelitis when they come into contact with the tissues of the central nervous system. These antibodies may be difficult to detect because they are intracellular.

The active Residue 1 material has been found to be active in producing a conversion from the tuberculin-negative to the tuberculin-positive state in guinea-pigs when used as 4 serial doses of 0·5 mg. homogenized with Bayol F, Falba and carbol saline. The papainized residue material was also active in producing this conversion in a dose of 1 mg. when similarly treated, but only a single injection was given.

The lack of activity found with the purified protein derivative in producing allergic encephalomyelitis is very likely due to some essential difference between the insoluble somatic protein of the tubercle bacillus and the soluble protein found in the culture media in which the bacillus has grown.

The reaction produced with the active fractions shows changes on the part of the mesodermal elements of the central nervous system, namely the blood vessels, the meninges and the microglia, as well as the ectodermal elements, namely the white fibres and the astrocytic elements. It seems probable that there is a specific stimulation to the microglia in these experiments and the striking lesions observed in the superior tela chorioidea may reflect an abnormal sensitivity in this region. In the control animals all that one can see here are a few glial cells and nerve cells but it is of interest to note that this is one of the sites described by del Rio-Hortega (1921, 1932) as giving rise developmentally to the fountains of microglia, and it is possible that in these animals the capacity to proliferate cells at these sites may persist into adult life and that the reactions seen in this region are evidence of this capacity.

Summary

(1) The tubercle bacillus has been fractionated in an attempt to identify the principle active in the development of experimental allergic encephalomyelitis when injected with homologous brain suspension.

(2) The materials extracted by prolonged treatment with lipid solvents are inactive.

(3) The activity remains with the residues left after such extractions.

(4) Digestion with papain for several days did not destroy the activity of these residues.

(5) Strong acid hydrolysis for 24 hours destroys the activity.

(6) It is therefore concluded that the main activity probably resides in the somatic protein of the bacillus.

(7) The formation of a complete antigen by the union of this protein with the lipid component of the brain acting as a hapten is suggested as underlying the genesis of allergic encephalomyelitis.

Acknowledgments

I have much pleasure in thanking Professor Sir Robert Robinson, *O.M.*, and Dr. N. Polgar for their kind assistance and advice. Also I am indebted to them for the preparation of the acetone soluble and isopropyl ether soluble and other lipid fractions. Dr. J. Ungar of Messrs. Glaxo has very generously helped by providing fractions and other assistance. Dr. H. H. Green of the Ministry of Agriculture and Fisheries has kindly prepared the purified protein derivative and other bacillary products.

Dr. L. E. Glynn has very actively assisted and advised me and I am very indebted to him indeed. Much of the technical histological work was undertaken by Mr. J. Dorling and the microphotography was performed by Mr. P. J. Fiske.

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LEGENDS FOR PLATES

PLATE VIII

FIG. 1.—Series 1–7. Section through fornix, showing marked microglial perivenular proliferation. The vessel wall shows some cellular infiltration. × 240 (Nissl's stain).

FIG. 2.—Series 1–7. Gross infiltration in the wall of a vein with surrounding slight microglial increase in the diencephalon. × 285 (hæmatoxylin and eosin).

FIG. 3.—Series 1–7. Section through the pons. Showing basilar artery and cellular infiltration around the vessels in the meninges. × 50 (hæmatoxylin and eosin).

FIG. 4.—Series 1–7. Showing round-cell infiltration in the meninges overlying the cerebral hemisphere. × 210 (hæmatoxylin and eosin).

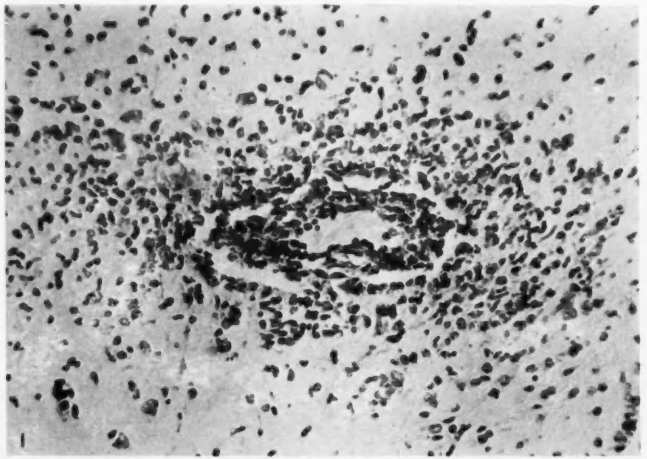
PLATE IX

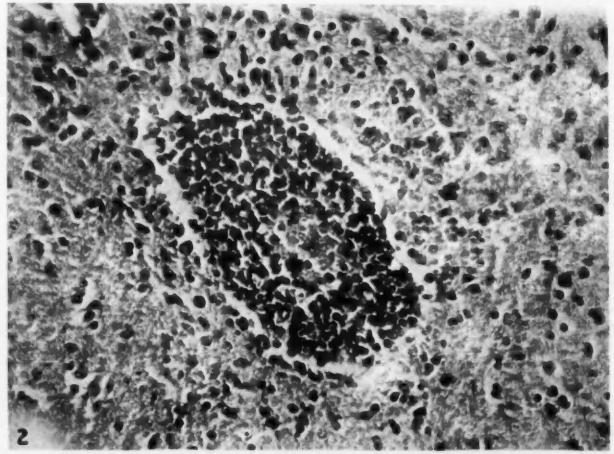
FIG. 5.—Series 1–7. Section through diencephalon and fornix. Showing granulomatous reaction in the meningeal fold and similar reactions in walls of adjacent blood vessels. × 90 (hæmatoxylin and eosin).

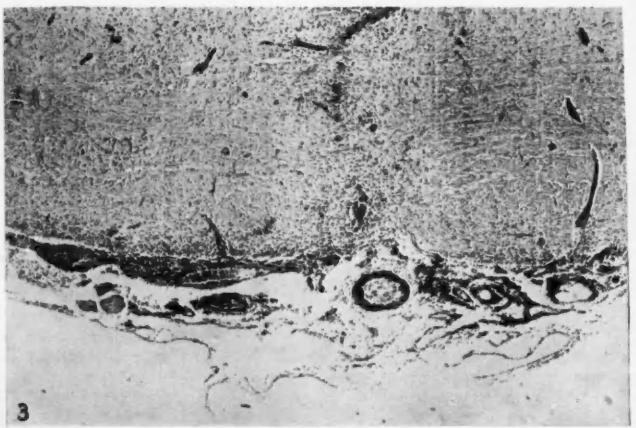
FIG. 6.—Series 1–7. Granulomatous reaction in superior tela chorioidea dorsal to the third ventricle. × 85 (hæmatoxylin and eosin).

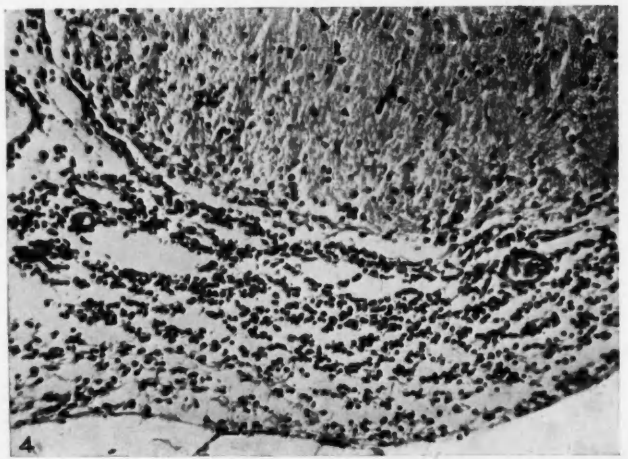
FIG. 7.—Series 1–7. High-power field from fig. 6. Shows two cells with large pale oval nuclei and vacuolated cytoplasm, probably histocytic cells. Some mitotic figures can be seen close by and numerous round cells. × 1,000 (hæmatoxylin and eosin).

FIG. 8.—Series 1–7. High-power field from fig. 6. Showing cells with flask-shaped and curved thick rod-shaped nuclei. × 1,800 (hæmatoxylin and eosin).



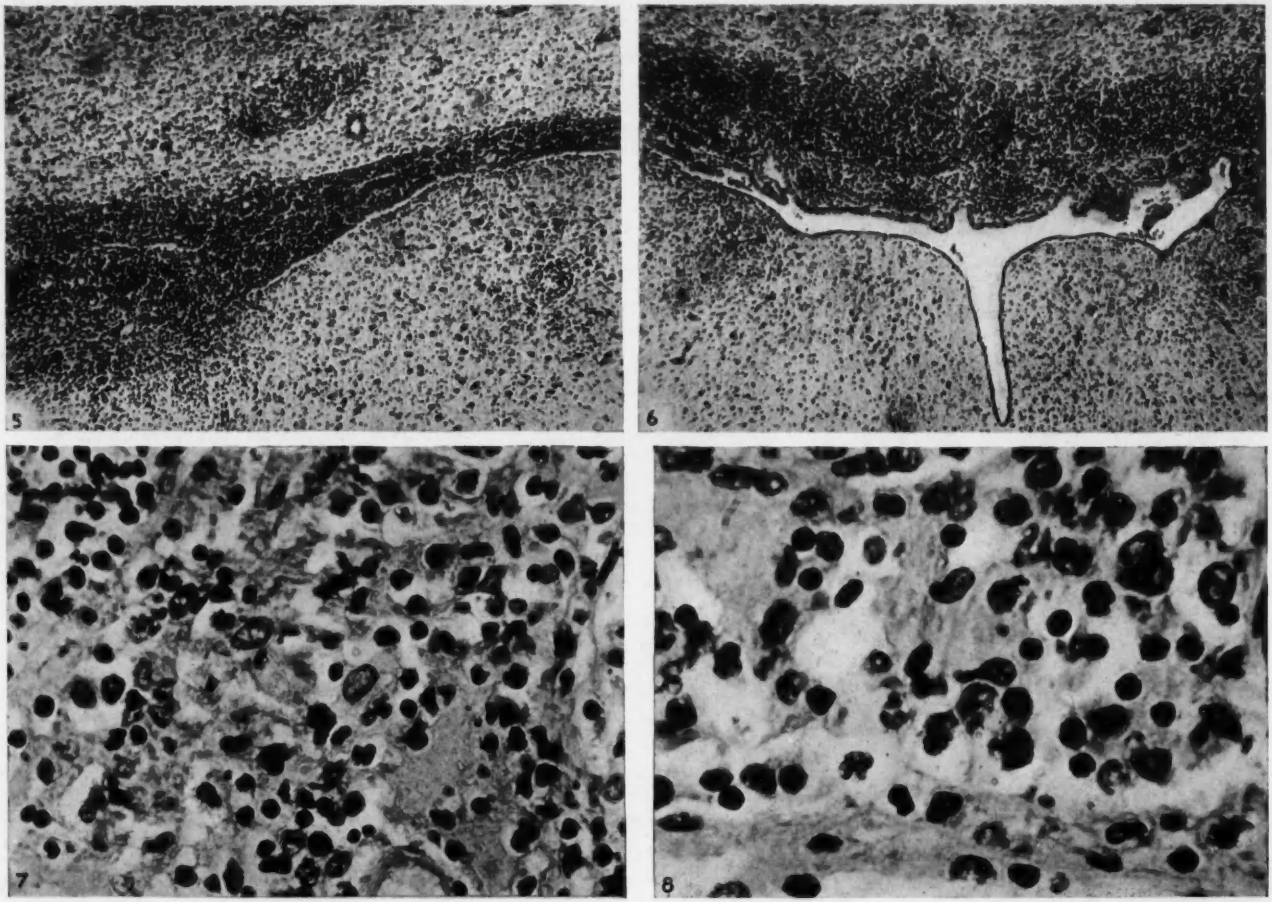






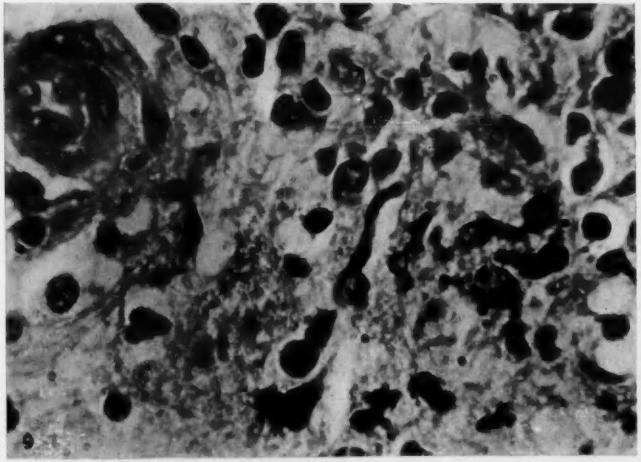
To illustrate article by J. Colover.

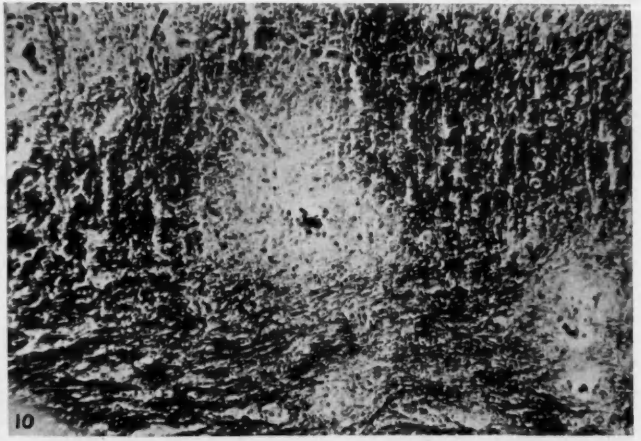
PLATE IX

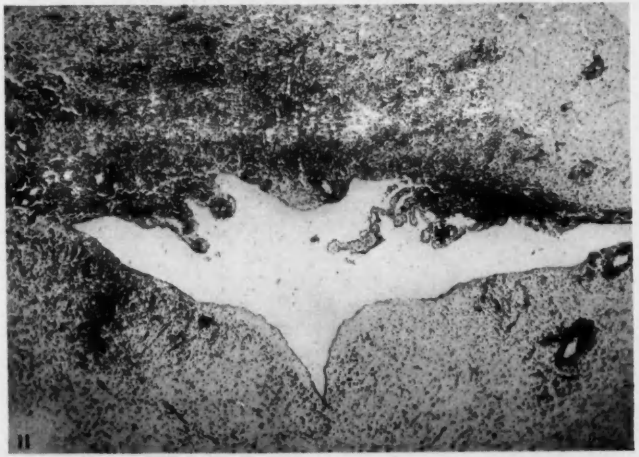


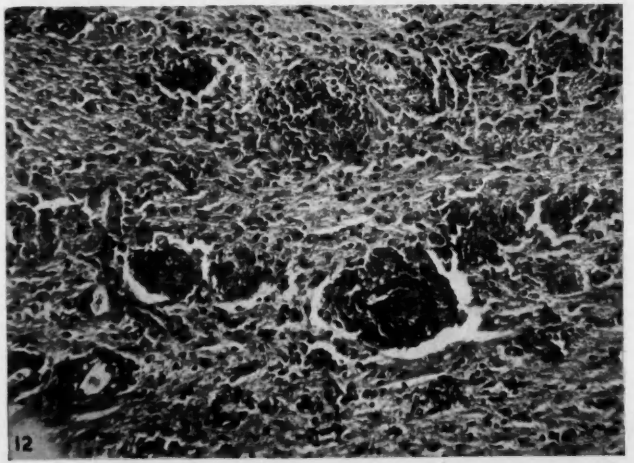
To illustrate article by J. Colover.

PLATE X









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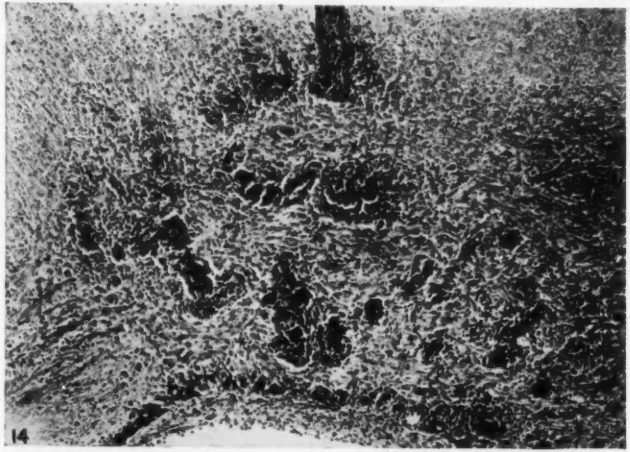

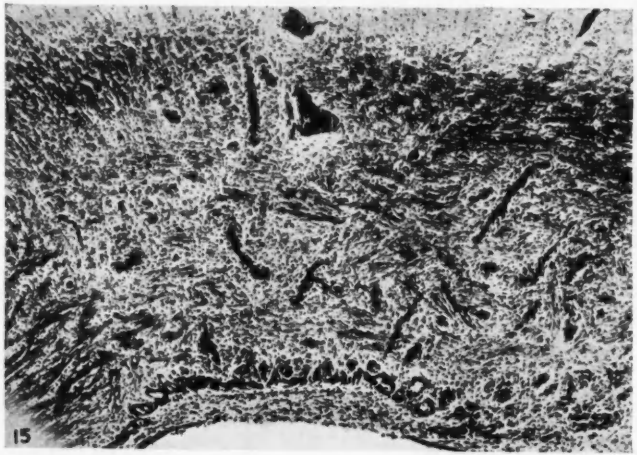

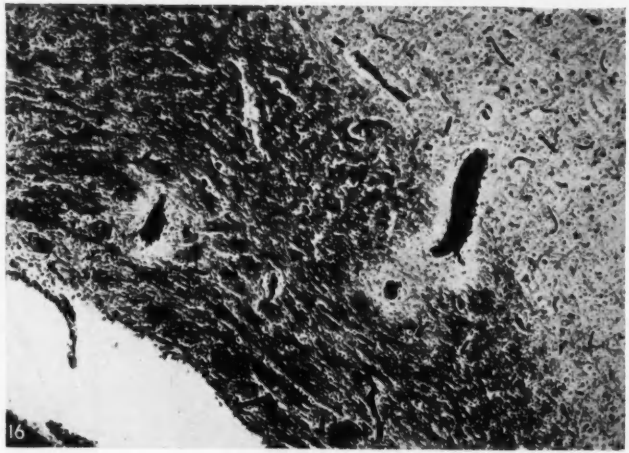

To illustrate article by J. Colover.

PLATE X

FIG. 9.—Series 1–7. High-power field from fig. 6. Shows a cell with an elongated narrow nucleus in the centre of the field with a transitional type of cell on the left-hand side. *See text.* × 1,800 (hæmatoxylin and eosin).

FIG. 10.—Series 1–7. Showing perivascular demyelination in the corpus callosum. × 185 (Loyez stain).

FIG. 11.—Series 3–3. Showing cellular reactions in the fornix and in the sites of attachment of the chorioid plexus of the third ventricle. A number of vascular lesions are also shown. × 50 (Nissl's stain).

FIG. 12.—Series 3–3. Granulomatous changes occurring in the venule walls in the corpus callosum. × 210 (hæmatoxylin and eosin).

PLATE XI

FIG. 13.—Series 3–3. Section through the diencephalon and column of the fornix showing granulomatous changes around the vessels in the meningeal fold and in the vessels of the fornix. Surrounding the latter is some microglial proliferation. × 50 (Nissl's stain).

FIG. 14.—Series 3–3. Showing granulomatous changes in the vessels of the radiation of the corpus callosum. × 80 (hæmatoxylin and eosin).

FIG. 15.—Series 3–3. Myelin stain of section made from same block as fig. 14 showing only partial myelin damage in this region. × 80 (Loyez stain).

FIG. 16.—Series 3–3. Showing perivascular demyelination in the corpus callosum. × 105 (Loyez stain).

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CEREBRAL CONTROL OF RESPIRATION

BY

ERIC A. TURNER

(*From the Queen Elizabeth Hospital, Birmingham*)

CONSIDERABLE interest and some controversy have centred during the last fifteen years upon the question of how visceral and "autonomic" functions are represented in, and affected by the structures of the cerebral hemispheres. Many of the earlier physiological investigations concerned the activities of the "centres" in the brain-stem, but, as has been frequently recounted, Spencer as early as 1894 conducted an investigation into the effect on respiratory and vascular functions of stimulation of various points in the cerebral hemisphere of cats.

He found that effects on the respiratory cycle in the form of apnœa could be obtained by electrical currents applied to the area of cortex corresponding with what we now know as the posterior orbital gyrus—Area 13 of Walker's map (Walker, 1940). He claimed that by cutting coronal sections progressively backwards in the living brain of the cat he could trace this effect backwards into the red nucleus. He also investigated increased action of the respiratory movements, which he classified as acceleration (from the sensorimotor cortex), over-inspiratory clonus (from the junction of the olfactory bulb and tract) and over-inspiratory tonus (from various sensory nerves and the "descending motor tract").

Munk in 1890 had described similar but less exhaustive observations on the effect of application of electrodes to the lower surface of the frontal lobes. Of numerous early observations on alterations of respiration following disturbance of cerebral structures but few add to the knowledge of where and when a constant result can be expected. Christiani (1885) investigated the diencephalon in rabbits and concluded that an inspiratory "centre" was present in the thalamus, close to the wall of the third ventricle and just in front of the corpora quadrigemina and the upper end of the aqueduct. After removal of the hemispheres and thalami he found that excitation of the corpora quadrigemina caused arrest in expiration and concluded that here was an expiratory "centre." Martin and Booker plunged electrodes into the substance of the mesencephalon,

and near the aqueduct produced acceleration of respiration which was changed into inspiratory arrest on applying a strong stimulus.

Numerous similar observations have since been made, and much discussion about "centres" has been conducted concerning the findings in the brain-stem and diencephalon. The last word can for the moment be left with Spencer in 1894. "I fail to see why the presence of 'respiratory centres' should have been assumed from these experiments, if the term 'respiratory centre' be used in anything like the same sense as when applied to the representation of respiration in the floor of the fourth ventricle. In fact, excitation experiments of this kind give results which are equally well or even better attributed to the results of stimulating fibres than of stimulating central mechanisms."

Knowledge of the effects of cortical stimulation advanced but slowly in the forty years following Spencer's work. A survey of the literature was given by Smith (1938) in the course of a report of his own. Like most of the previous investigators in this field he was concerned with electrical stimulation of the precentral gyrus (Areas 6a and 6b) or its equivalents, but he found similar responses from corresponding areas in the cat, dog and monkey and concluded cautiously enough that this suggested "the existence of a fundamental plan for the cortical control of respiration in the general scheme of cerebral cortical evolution."

Interest in the orbital surface of the frontal lobe was revived by Bailey and collaborators. With Bremer in 1938 Bailey found that stimulation of the central end of the vagus nerve increased the electrical potentials of this part of the frontal cortex. In 1940 Bailey and Sweet investigated the effects of stimulation of the orbital surface of the frontal lobe in cats and monkeys. They found that an area in the gyrus orbitalis near the olfactory tract gave rise in both species to inhibition of respiration, rise of blood pressure and decrease in the tonus of the gastric musculature. All these effects were more marked in the monkey than in the cat, while accessory effects on the muscles of the tongue, jaws and fauces were noted in the cats but not in the monkeys.

Several papers followed this work, confirming it, and adding new information. Delgado, Fulton and Livingston (1947) showed that points could be found in the orbital surface which caused a *fall* in blood pressure as well as respiratory arrest. Sachs and Brendler (1948) had found that the areas causing the two effects could be accurately localized, while they showed that arrest of respirations could be induced at any phase of the respiratory cycle.

The scope of experiment was gradually extended. First, it had been noted by Smith (1941, 1945) that respiratory inhibition as well as other

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effects (and independent of these other effects) could be obtained by stimulation of the cingulate region in the monkey. The response included vocalization, facial expressions, and inhibition of skeletal muscular tone and movements. Secondly, "physiological neuronography" by means of strychnine showed reciprocal firing between the posterior orbital surface and the cortex of the temporal pole (Bailey *et al.*, 1944). Thirdly, studies of cortical cytoarchitecture indicated a similarity of structure between these two areas (von Bonin and Bailey, 1947; Bailey and von Bonin, 1951), which were also closely related to the "allocortex" of the cingulate or limbic region.

Actuated by such considerations Kaada, Pribram and Epstein (1949) investigated widely in and around all these regions, and found that similar respiratory and vascular responses could be obtained from a continuous area of cortex from the rostral limbic gyrus through the subcallosal region, posterior orbital surface, anterior perforated space, and anterior parts of the insula to the uncus and temporal pole. They pointed out that all of this area consisted of allocortex, of transitional sensory cortex ("juxtallocortex"), or of transitional motor cortex ("mesocortex").

Ablation experiments were performed on these areas of cortex. Livingston, Fulton *et al.* (1947) attacked the posterior orbital region of cortex so as to remove Walker's area 13 in monkeys. As a result the contralateral limbs showed a rise of temperature and a more rapid reflex dilatation under appropriate changes of temperature. No change in respiratory function was noted.

Ward (1948) ablated the cingulate gyrus in monkeys, and reported that thereafter they showed loss of fear of man, social indifference to their fellows, and loss of mimetic activities, grooming, and signs of affection. There had apparently been an "emotional bleaching."

Ablation of temporal structures was performed, but the experiments were so complicated by damage to or removal of several parts at once that results would have been difficult to interpret even if they had not been contradictory and performed on different species.

A further complicating factor was introduced. Ruch and Shenkin (1943) found that after bilateral ablation of Area 13 their monkeys were "hyperactive." The appearance of hyperactivity, or hyperkinesis, had been studied after various forms of frontal ablation in cats and monkeys, and it was clear that the same phenomenon was being described by different workers, though details of description varied. According to Ruch and Shenkin it was manifested in the monkey by long-continued methodical pacing of a regular, stereotyped character. In 1938 Richter and Hines had shown that bilateral removal of Brodman's Area 9 produced an increase in

kinesis, but the factor which consistently resulted in a gross increase was damage to the anterior end of the caudate nucleus and putamen. This idea, which had long been held, was thus given firm experimental confirmation. It was further confirmed by Mettler and Mettler (1942) and F. A. Mettler (1945), who added numerous details to the description of the forms of hyperkinesis shown by the monkey with striatal damage.

In 1951 Davis concluded that only those animals which had sustained primary or secondary damage to the head of the caudate nucleus showed significant hyperkinesis. He suggested that this was true of other frontal areas, and pointed out that the damage need not be direct, but might act through the vascular supply. Indeed, he claimed that vascular impairment to the head of the caudate was an "almost invariable consequence" of operative ablation of Area 13. In a comprehensive account of all aspects of the problem up to that time, he described his attempts to assess subtle degrees of impairment of respiratory adjustment by testing his animals (monkeys) under conditions of low atmospheric pressure before and after operation.

It was from this point that the present study began. In an endeavour to shed light on the controversial issues involved, it was determined to investigate the same problems by means of a different experimental approach. Since it had proved difficult to destroy or remove Walker's Area 13 without affecting primarily or secondarily the head of the caudate and the neighbouring striatum it was planned to use two series of animals. In one series the tracts leading downwards from Area 13 to the caudal structures (the diencephalon and brain-stem) were to be destroyed, preferably by selective electrolytic lesions, while in the second series the head of the caudate was to be destroyed without damage to the underlying cortex of Area 13. The two series were to be compared by tests which would correspond as closely as possible with those used by previous observers. By such means it was hoped that some measure of proof would emerge in favour of one or other of the hypotheses advanced by the previous workers.

The first difficulty was that no certain knowledge existed concerning the descending pathways from Area 13. Wall, Glees and Fulton (1951) reported that a fine fibre connexion ran from this area to the hypothalamus and also to the upper part of the head of the caudate. (The connexion with the hypothalamus was confirmed by Beck, Meyer and Le Beau (1951), while by means of strychnine "neuronography" Sachs, Brendler and Fulton (1949) had obtained firing in the hypothalamus, the H field of Forel, the homolateral and contralateral putamen, and a small region of the internal capsule, as well as in the contralateral Area 13 and the contralateral caudate nucleus.) In the report by Wall, Glees and Fulton (1951), Wall reported

that discrete lesions in the hypothalamus abolished the effect of stimulation of Area 13 in so far as the blood pressure was concerned, but left intact the respiratory effects. On the other hand stimulation of the head of the caudate caused respiratory changes, but only minimal changes in the systolic blood pressure. The conclusion to be drawn was that the respiratory effects might be carried by fibres which ran via the caudate nucleus. If this were the only descending pathway obviously the experiments in the present study would be doomed to failure.

First, therefore, it was necessary to investigate by a series of acute experiments the various diencephalic structures and pathways, which might carry the descending fibres, and very soon it was decided to narrow the field of study to the respiratory effects, and in particular respiratory inhibition. This restricted field of study met with positive results, and it was concluded that the descending pathway carrying this particular inhibitory effect could be consistently destroyed without causing any damage to the head of the caudate nucleus.

The two series of chronic experiments were accordingly undertaken. In order to have as many opportunities as possible of cross-checking the information, various control animals were used, using similar methods of testing and operating, but on different anatomical structures. Finally, it was obvious that the material should be used in such a way as to shed any possible light on the essential functions of the parts concerned. Accordingly, the same structures were studied with stimulation of the fully recovered animals by means of indwelling electrodes. (This was done in collaboration with J. Delgado, and will be published elsewhere.) Those animals which had lesions of the head of the caudate without damage to the underlying cortex were subjected to a special neurological observation, and will also form part of a separate study (in collaboration with G. Davis and T. Twitchell). Several animals were sacrificed after a short interval of time so that anatomical studies by means of silver impregnation could be used to investigate non-myelinated fibres. These investigations are at present under way.

Part I

Acute experiments.—In this part of the work 3 cats and 16 immature rhesus monkeys were used, the cats being first operated upon until the technique was satisfactory. In the course of the experiments 162 stimulations were administered to the cats, and 1,598 to the monkeys. A general map-like survey was followed by destructive lesions in what might be descending pathways, followed by re-elicitation of the same effect (apnœa) from higher points. In every case the effect was compared with the mirror point on the other side to eliminate possible effects of deepening anæsthesia or deterioration in the animal's condition.

The stimuli used were 0·2 ms. 40 c. per sec. square waves balanced to result in

alternating current. (A pure direct current square wave gave inconstant results probably from polarization.) Strength up to 8 V. Longer pulse durations with a smaller frequency gave similar effects but were not extensively used.

It would be impossible to reproduce details of over 1,500 stimulations and observations, so recourse must be had to a summary of the findings, which are:

A. Stimulation of the following anatomical structures or points consistently produced apnœa in the lightly anæsthetized animal:

The posterior orbital gyrus (A 22, L 6·5, H 1 mm. above base); "prethalamic bundle" (A 12·2, L 1·5, H+4); amygdaloid nucleus (12·2, 11, −2); ansa lenticularis (10·3, 2·5, +1); zona incerta (8·2, 2·5, +1); n. medialis dorsalis of thalamus 5·2, 2, + 5); n. centrum medianum (3, 4·5, + 2·5); stria medullaris (10·3, 1 + 7, and 5·2, 0·5, +7); habenular nucleus (0·7, 1·5, +5); habenulo-peduncular tract (5·2, 2, − 1); "submedian" reticulum (1·8, 3, − 2); rostral edge of pes pedunculi (8·2, 4, −5).

Results from motor cortex and its descending pathways were not tested other than in the pes pedunculi as above. From the hypothalamus panting could be produced, but no consistent apnœa. From the amygdala panting was occasionally produced, as it was also from the olfactory cortex. The apnœa produced from the stria medullaris, the habenular nucleus and the habenulo-peduncular tract seemed to be due to excessive stimulation of expiration, and very mild stimuli would produce effects of expiratory straining, a counterpart of the "over-inspiratory clonus" of Spencer.

B. By means of destructive lesions in the caudal structures and retesting of the structures lying rostrally it was demonstrated with greater or less probability that:

(1) The apneustic effect of stimulation of the posterior orbital gyrus could be abolished by a single lesion in the "prethalamic bundle" of the same side; or by two lesions, one in the ipsilateral subthalamus, the other in the pes pedunculi (*see figs.* 1–6). These results seemed reasonably well demonstrated in several animals.

(2) The amygdaloid effects were abolished by similar combined lesions. This was less certain, as no experiments were designed to demonstrate this point exclusively.

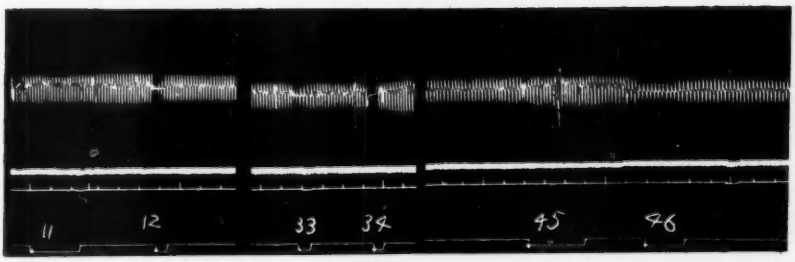

Fig. 1.—*Acute Monkey No.* 11. Recording of respiratory records (inspiration downwards) with time in seconds, with 10 second and minute intervals in all figures. Hypopnœa occurs at Stimulus 12 applied to the left posterior orbital gyrus. There is still hypopnœa from the same point (Stimulus 33) after destruction of left stria medullaris and after one lesion in the left zona incerta; also apnœa from the left "prethalamic bundle" (S.34). After further destructive lesions of the left zona incerta there is still hypopnœa from stimulation of the left prethalamic bundle (S.45) and the left amygdala (S.46).

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(3) The effects in the stria medullaris, habenular nucleus, and habenulo-peduncular tract could not be traced as far as the interpeduncular nuclei. Similar effects could, however, be obtained from the reticulum of the mid-brain just caudal to the habenulo-peduncular tract and the presumption was that the effector fibres passed into the reticulum and did not go to the interpeduncular nuclei.

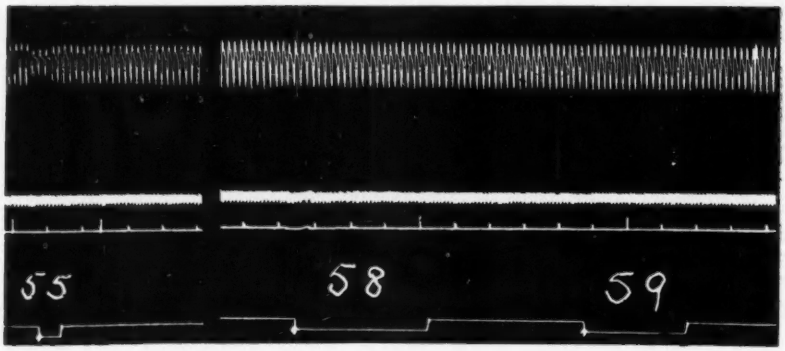

Fig. 2.—*Acute Monkey No.* 11. After destruction of the whole of the left zona incerta there is still some hypopnœa on stimulation of the left posterior orbital gyrus (s.55). There is, however, no effect from stimulation of the left posterior orbital gyrus (s.58 and s.59) after destruction of the left prethalamic bundle.

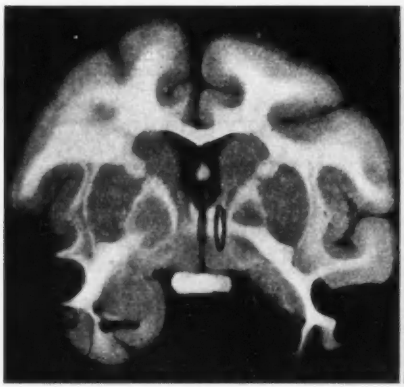

FIG. 3.

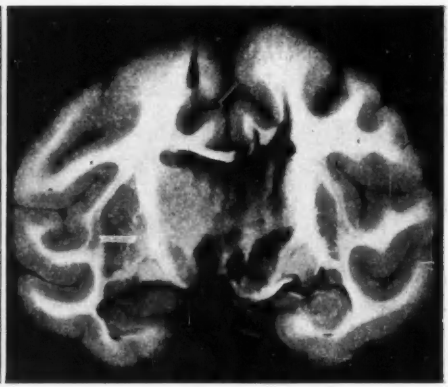

FIG. 4.

Fig. 3.—Slice of brain of macaque cut in the vertical Horsley Clarke plane. The black line contains an area in which descending fibres from the posterior orbital gyrus are believed to run ("prethalamic bundle").

Fig. 4.—Slice of brain of Acute Monkey No. 11, to show destructive lesions in the Horsley-Clarke plane A. 8·0 mm. approximately (subthalamus, stria medullaris, ansa lenticularis and cerebral peduncle).

(4) It was impossible to abolish the effect of the thalamic nuclei without destroying both the mid-brain reticulum and the pes pedunculi: i.e. producing in effect a hemisection at the mid-brain level.

C. Figs. 7, 8 and 9 illustrate certain observations which seem worthy of record. The legends explain the points, which will not be repeated here.

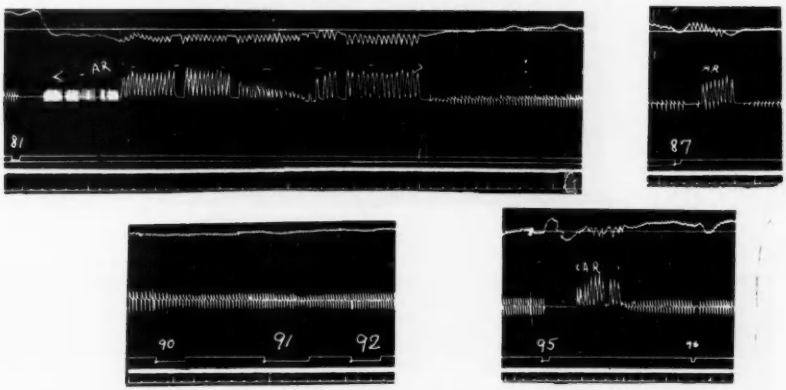

Fig. 5.—Acute Monkey No. 11. Recordings of respirations and blood pressure. After destruction of the *left* prethalamic bundle and the *right* ansa lenticularis (No. 4), brief stimulation of the right posterior orbital gyrus (S.81) produces such profound apnœa that artificial respiration is necessary for 5¾ minutes. After destruction of the right stria medullaris (No. 6) there is still gross apnœa from brief stimulation of the right amygdala (S.87). After destruction of both the right ansa lenticularis and the right pes pedunculi (No. 7) stimulation of the right posterior orbital gyrus (S.90) produces no appreciable effect on respiration or blood pressure. There is still a minimal effect obtainable from the right amygdala (S.91), but none from the right prethalamic bundle (S.92). There is still a gross effect obtainable from the left N. ventralis posterior thalami (S.95) and from the same nucleus on the right side (S.96).

Whenever a critical amount of the upper brain-stem had been destroyed or a critical degree of apnœa had been reached the effect of stimuli on respiration gradually vanished from all supratentorial structures leaving only the effects obtainable in the mid-brain and medulla. Finally, only the medullary effects could be obtained. The disappearance of these effects from the rostral structures occupied about an hour. It seemed that medullary respiration alone in the monkey was insufficient to maintain function in supratentorial structures. (The importance of this observation to higher members of the primates, including Man, especially with respect to head injuries, tentorial pressure cones, and other brain-stem lesions will be immediately apparent.) After destruction of mid-brain reticulum a fall in blood pressure, bradycardia, and an increased rate of respiration could still be obtained by stimulation of the periaqueductal grey. This was the nearest approach to the hyperpnœa seen in human cases of tentorial pressure cones that was obtained in this series of experiments. (As long ago as 1923 Walshe suggested that extensor spasms in human cases might be due to direct excitation by anoxia of grey matter in the brain-stem. *See* James and Turner, 1951. Fig. 10.) Destruction of the periaqueductal grey did not abolish the effects of stimulation of the amygdala subthalamus or stria

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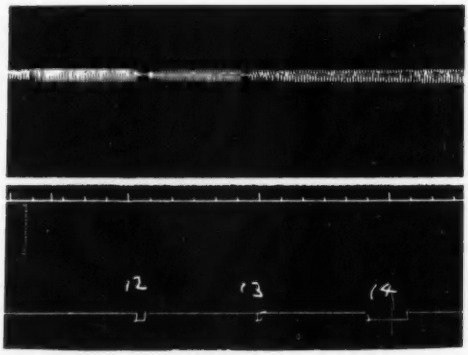

FIG. 6 (a).

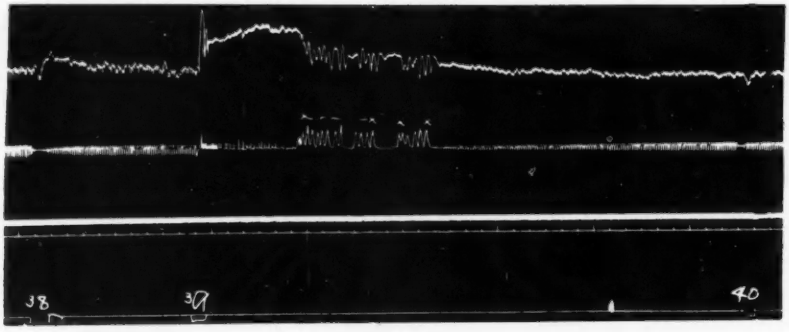

FIG. 6 (b).

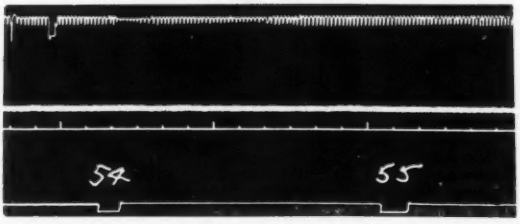

FIG. 6 (c).

Fig. 6.—Acute Monkey No. 14. (a) Stimuli to the right (S.12) and left (S.13) posterior orbital gyri result in apnœa. (b) Hypopnœa can be seen on stimulation of the right posterior orbital gyrus (S.38, 40), just before a destructive lesion of the right prethalamic bundle. Brief stimulation of the right prethalamic bundle (S.39) results in prolonged hypopnœa requiring artificial respiration for one and a half minutes. The blood pressure is elevated by the stimulation. (c) After destruction of the *right* prethalamic bundle stimulation of the *left* posterior orbital gyrus still produces hypopnœa (S.54) whereas stimulation of the *right* posterior orbital gyrus has no effect (S.55).

medullaris, though the disturbance to respiratory function was so profound that all supratentorial effects gradually faded out.

Part II

As a result of the acute experiments described in Part I it was concluded that the effector pathways from Area 13 ran as depicted in fig. 13. As far as the anterior end of the subthalamus all the fibres appeared to be localized to a small area. (It was not felt justifiable to identify this pathway with any previously defined anatomical structure, and the descriptive term "pre-

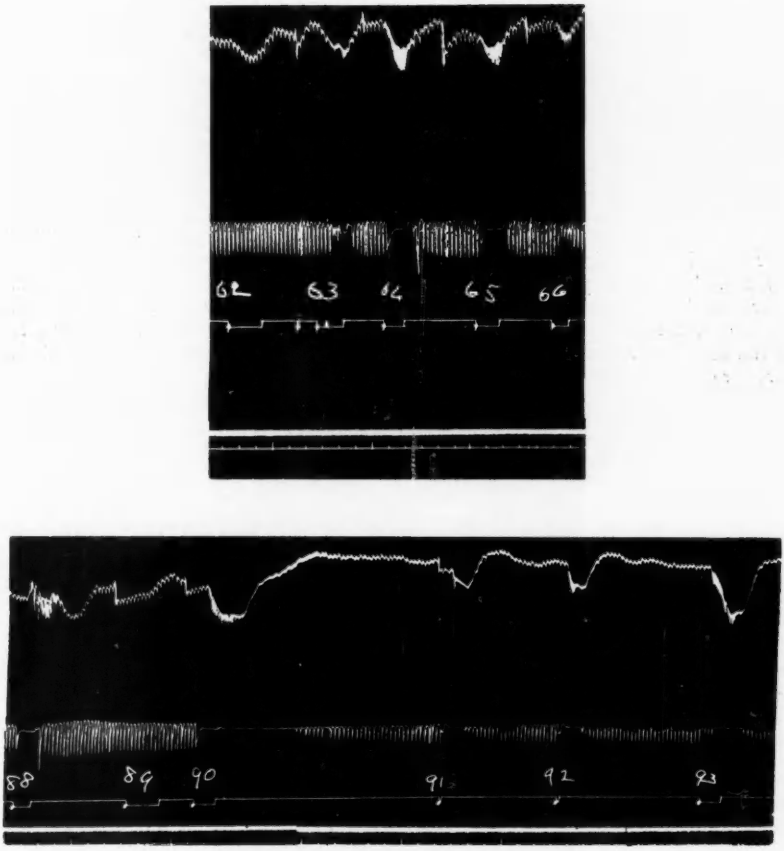

Fig. 7.

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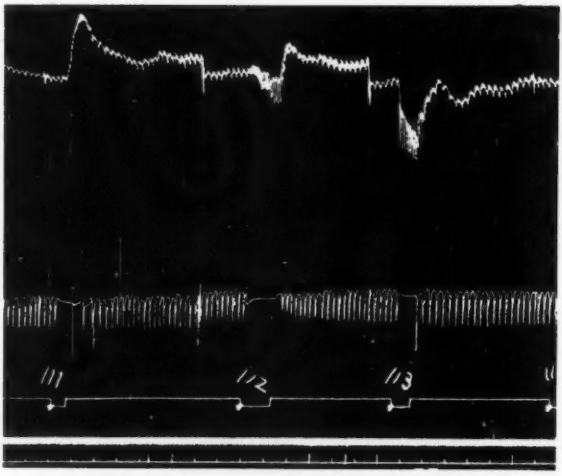

FIG. 7 (*contd.*).

Fig. 7.—*Acute Monkey No.* 2. Stimulation of central grey (S.64, 65), field of Forel (S.88), habenulo-peduncular tract and the reticulum surrounding it (S.90, 91, 92, 93). The blood pressure falls in all of these and there is bradycardia and an increase of pulse pressure (just as in a "fainting attack"). By contrast stimulation of the N. dorsalis medialis thalami (S.111) produces a rise of blood pressure and a rise of pulse pressure. Stimulation of the amygdala (S.113) causes a fall of blood pressure and bradycardia like the reticular substance.

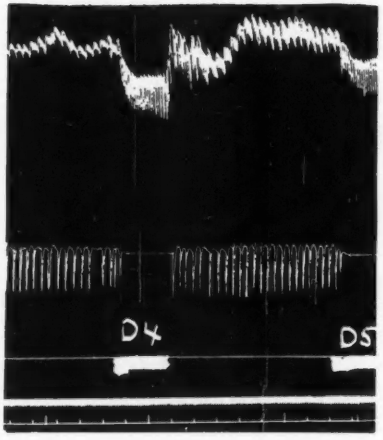

Fig. 8.—A direct destructive current passed (D.4) into the reticular substance of the brain-stem caused the same effect as a square wave stimulus.

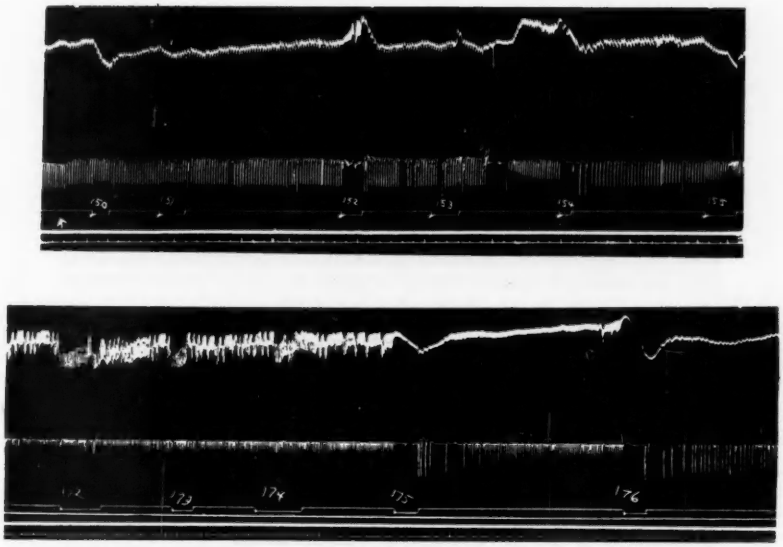

Fig. 9.—After the respiratory effect has been abolished from the stria medullaris by a destructive lesion the effect on the blood pressure remains (S.150). After a destructive lesion in the reticulum of the mid-brain stimulation of the N. ventralis posterior thalami (S.152) results in only hypopnœa, but the rise of blood pressure is still brisk, and is accompanied by an increase in pulse pressure. Stimulus applied to the N. *centrum medianum* thalami (S.154) results still in apnœa and a fall in blood pressure. Respiration remains slow for several minutes. After gross destruction of the mid-brain reticulum stimulation of the amygdala (S.172, 173) produces no effect on respiration but a fall in blood pressure. Stimulation of the centro-median nucleus (S.175) and of the postero-ventral nucleus (S.176) still cause apnœa and now a fall in blood pressure.

thalamic bundle" was used when referring to these fibres.) Caudal to the anterior end of the subthalamus the pathway appeared to bifurcate.

These facts led to the performance of the following chronic experiments.

Eighteen immature rhesus monkeys were examined and tested before and after operation in ways which will be described below. Three of these animals were given electrolytic lesions in the "prethalamic bundle" by the stereotaxic technique, the point being checked at the times of operation by means of stimulation to ensure that it was indeed an apneustic one. This was necessary as movement of 1 mm. would abolish the effect, and the instrument had an error of this degree from one animal to another. Four animals had similar, though larger, lesions placed in the head of the caudate nucleus on both sides, or in the case of one of them on only one side. One of these animals died as a result of its own hyperkinesis, so three were left for comparative study. Three animals had lesions placed bilaterally in

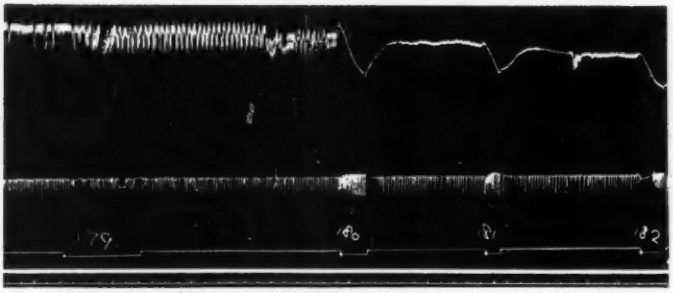

Fig. 10.—After gross destruction of the mid-brain reticulum stimulation of the hypothalamus (S.179) produces irregular respirations, a transient slight fall in blood pressure, bradycardia and an increase in the respiratory fluctuation in blood pressure. Stimulation of the central grey (S.180, 181) results in panting followed by apnœa after the stimulus ceases. There is a brief rise in blood pressure followed by a profound fall.

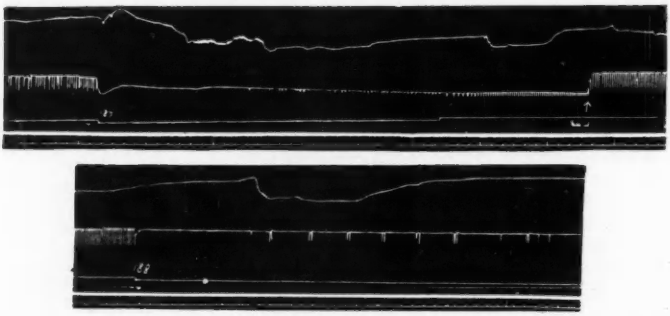

Fig. 11.—Prolonged stimulation (S.187, 188) of the mid-brain reticulum results in apnœa lasting for two minutes, followed by profound depression of respiration for another five minutes. The "escape" is insufficient to preserve life.

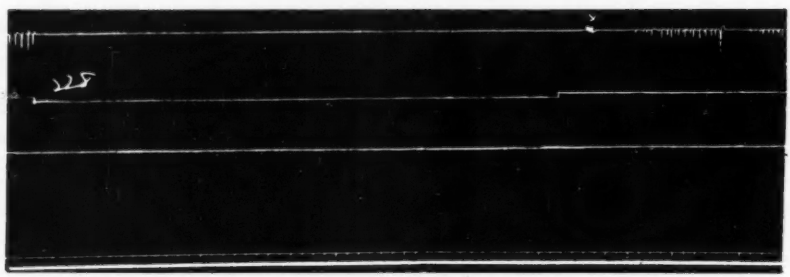

Fig. 12.—*Acute Monkey No.* 3. Apnœa for seven minutes results from stimulus to the lateral end of the zona incerta (S.228). Similarly prolonged effects were seen in different animals from stimulation of the centro-median nucleus of thalamus, the stria medullaris, the prethalamic bundle and the pons. Sometimes these prolonged effects resulted from stimulation lasting only 2 to 3 seconds.

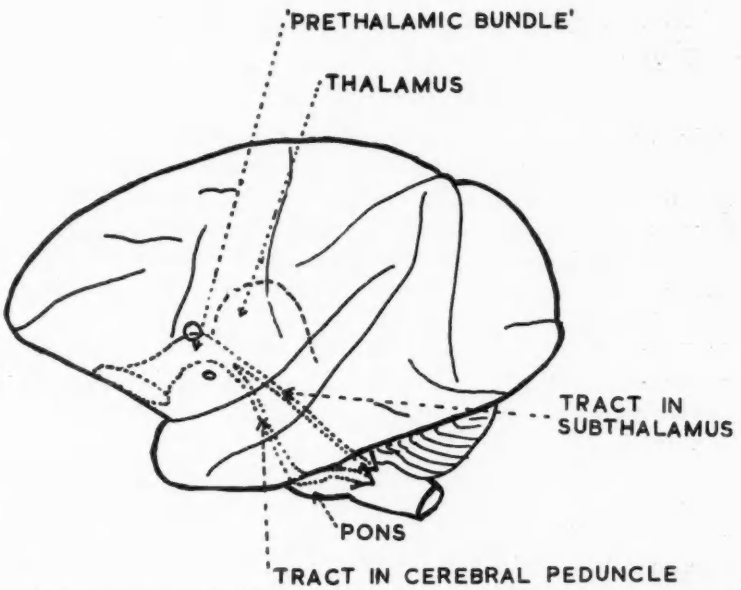

Fig. 13.—Diagram indicating pathways by which, it is suggested, impulses from "Area 13" reach the reticulum of the brain-stem.

the region of the amygdaloid nucleus, three had no lesions but had implanted electrodes inserted into the same spots as were being studied, and the remaining four had each different lesions, one in Area 13, one in the subthalamus, one in the centro-median nucleus of the thalamus and one in the mid-brain reticulum at the apneustic point (all of these lesions being bilateral). Finally, a hemispherectomy was performed on one animal, which died six days after operation. All the remaining animals were sacrificed when their tests were completed, some early so that the brains could be tested for tract degeneration, others after four months' observation. In each case the brains were sectioned serially either by frozen section or after embedding in celloiden.

Kinesis—Significant Somatic Movements

The animals were tested in cages in the fashion described by Davis (1951). One side wall of the cage was composed of two condensers, the capacitance of which varied with any significant movement of the animal. Each change of capacitance tripped a trigger mechanism in a battery of electrical counters. It was thus possible to read the kinesis of the animal for each hour of 24, the animal being kept meanwhile in a sound-proof box in a thermostatically controlled, air-conditioned room, itself soundproofed. It was confirmed, however, as Davis had found, that a

three-hour period gave consistent results, and in general the shorter period was employed.

Resistance to Anoxia

Before and after operation the animals were subjected to anoxia in a cage enclosed in a low-pressure chamber, such as is used for testing aviators. They were considered to be suffering from the effects of anoxia when they failed to perform a previously taught conditioned reaction. In response to the sounding of a bell at one end of the cage, or a buzzer, at the other, the animals had been trained to move away, or stay away, from the end from which the sound emanated.

While the "flight" was in progress only audible stimuli were employed so that the end-point could be considered to involve the "highest centres," and certainly required memory of what was expected, although the reason for it might be forgotten.

A noteworthy point was that once anoxia had supervened the cause of failure to obey the signal correctly varied from one animal to another. Sometimes the animal became confused, sometimes it would not bother to move, sometimes it tried to move correctly but fell on the way and would not, or could not, continue. Any one of these reasons constituted the end-point, though the signal was always repeated once as a single failure was sometimes found to be insignificant. Vomiting frequently preceded failure in the test by many minutes and by many thousands of feet.

One particular difficulty arose in connexion with those animals which were hyperkinetic by reason of lesions in the head of the caudate nucleus. These animals paced continuously irrespective of the bell or buzzer. Only when they began to become lethargic from anoxia did they cease pacing. Then they obeyed the signal correctly, so that it seemed that it was not abolition of memory that had occurred but failure to inhibit the pacing activity. Nevertheless in these cases the end-point was extremely difficult to determine, and was much more open to fallacy than in any of the other animals.

The pattern of the "flight" was that devised by Davis (1951). It was not necessary to modify the pattern in any way, so that strictly comparable measurements were made in every instance (fig. 14).

Comparison of Kinesis and Resistance to Anoxia

In the tables are given the detailed results of tests in the different groups of animals. It will be seen that so far as the results are significant in these small groups they demonstrate that there is no correlation between

TABLES OF RESULTS IN CHRONIC EXPERIMENTS—TABLE I

Site of lesion in Animal	*Day from operation*	*Kinesis*	*Ceiling (K = 1,000′)*	*Wt. (kilo)*
Caudate	51	269		
1	49	144		
	48		20K 6m	
	43	150		
	41	160		
	40	116		
	37	230		
	−9			3·05
Operation	+9	36		
	10	8		3·0
	14		20K 8m	
	16	53		
	17	510		
	20	1,118		2·9
	22	784		
	29	1,131		
	38	659		
	43			3·2
	84		25K	3·4
	115	1,225		3·8
Caudate	14	68		
2	12	28		
	10	78		
	8	65		
	7		26K	
	−2	223		2·25
Operation	+12	502		
	13		26K	
	20	325		2·6
	27	491		2·6
Caudate	11	292		2·0
3	10		24K	
	9	140		
	−6	100		
Operation	+3	303		2·2
	4		15K 30m	
	7	948		
	14	942		
	17		20K 10m	
	27			2·2
Prethalamic	11	106		
1	10		23K	
	9	143		
	8	113		
	4	276		2·5
	2	166		
	−1	180		
Operation	+4	167		2·85
	17	257		
	18	237	15K 15m	
	20	184		
	21	263		
	26	193		
	85		20K 17m	
	117	240		3·4

a profound rise in kinesis (in the caudate group) and a disturbance of the resistance to anoxia (in the group with lesions in the "prethalamic bundle"). In the latter group, two animals showed an extensive *rise* in resistance to anoxia in two tests within three weeks of each other. It appears that this is likely to be significant, as such a rise did not occur in other animals if the tests were as close together in time. A rise in resistance might occur with increased growth over the course of many weeks, but was never so great. (In interpretation of a rise the graph of the "flight" should be remembered, as the animal had to spend half an hour at 20,000 feet before going on. Many animals failed during this half-hour.) One animal in the "prethalamic" group had a fall in resistance, but it was suffering from pulmonary tuberculosis, so the result must be discounted. (No other animal in the series had tuberculosis at autopsy, which was performed in full in

TABLES OF RESULTS IN CHRONIC EXPERIMENTS—TABLE II

Site of lesion in Animal	*Day from operation*	*Kinesis*	*Ceiling (K = 1,000')*	*Wt. (kilo)*
Prethalamic	6	26	20K 16m	2·2
2	5	45		
	−4	96		
Operation	+14		28K	
	15	12		
	16	12		
	17	12		2·3
	20		28K	
Prethalamic	16		20K 23m	
3	13	63		2·2
	12	93		
	−6	30		
Operation	+6	93		
	8		27K	
	13	97		2·5
	19	105		
Amygdaloid	69		20K 1m	
1	64	374		
	63	312		
	62	391		
	60	651		
	58		20K 1m	
	55	516		
	52	637		
	47	599		
	−4			2·65
Operation	+4	146		
	7	308		
	10	446		
	11	439		
	13	530		
	14		23K	
	17	460		
	38			3·5
	119	615		

Site of lesion in Animal	*Day from operation*	*Kinesis*	*Ceiling (K = 1,000')*	*Wt. (kilo)*
Amygdaloid	7		25K	
2	6	14		1·65
	5	30		
	−4	16		
Operation	+14	53	24K	
	15	31		2·1
	16	122		
Amygdaloid	12	197		2·4
3	11	286		
	9	167		
	−2		28K	
Operation	+7	305		2·5
	8		21K	
	13	427		2·6
	16	325		
	20		29K	
Area 13	−1		20K 1m	
Operation	+33	14		
	38	13		
	44		26K	
	45	12		
Subthalamus	17		20K 25m	
	16	170		1·8
	14	100		
	−11	280		
Operation	+4	893		2·1
	9		20K 20m	
	10	873		
	17	1,000		2·15
	29			2·7

every case.) The "Area 13" animal showed a rise of resistance although it was never a vigorous animal after its operation and was certainly not hyperkinetic. (The lesion had, as it happened, not affected the caudate head.)

In the caudate group one animal had an extensive rise in resistance eighteen weeks after the first test, an intermediate test being identical with the first. This animal had become so muscularly strong by reason of its constant exercise, and had put on so much weight, that an increase

TABLES OF RESULTS IN CHRONIC EXPERIMENTS—TABLE III

Site of lesion in Animal	*Day from operation*	*Kinesis*	*Ceiling (K = 1,000′)*	*Wt. (kilo)*
Centro-median nucleus Operation	16	58	15K 7m	
	14	116		
	−12	105		
	+8	126		
	9		20K 1m	
	12	265		2·0
	17	261		
	29			2·1
Mid-brain reticulum	23		20K 7m	
	−16	84		1·7
Operation	+5	303		1·9
	8		26K	
	12	182		
	17	224		
	25			2·3
Implanted electrodes (various) 1	29	42		
	24		25K	
	23	30		
	22	59		3·3
	21	104		
	14	141		
	−13	73		
Operation	+25		23K	
	59		24K	
	68	206		
Implanted electrodes 2 Operation	4	317		3·7
	−3	222		
	+20		20K 1m	
	44		23K	
	63	742		4·4
Implanted electrodes 3 Operation	38	93		
	37	159		1·8
	35	88		
	−13		24K	
	+20		28K	
	30	312		2·1

of general fitness might account for this otherwise anomalous reading. The miscellaneous group had lesions in areas which could have affected either respiratory pathways, or descending pathways from the caudate or both, so no interpretation is possible of the group as a whole.

NEUROLOGICAL SIGNS

The caudate group will form part of a separate study. The other animals were also examined neurologically, and some results noted.

"Prethalamic" group and Area 13 (fig. 15).—This group of animals recovered consciousness quickly (by the evening of the operation). There was no abnormality of temperature. In one of them redness of the face, particularly round the nose, was noted (c.f. the Area 13 animal below). On the whole the group was an aggressive one, and aggression was noted as excessive in two of them.

One (fig. 15A) was particularly interesting in that it developed asthma after the operation. When examined in the chair this was an aggressive but not outwardly excitable monkey. She phonated normally with gutturals and chattering; but no screams or falsetto cries were heard. She did not

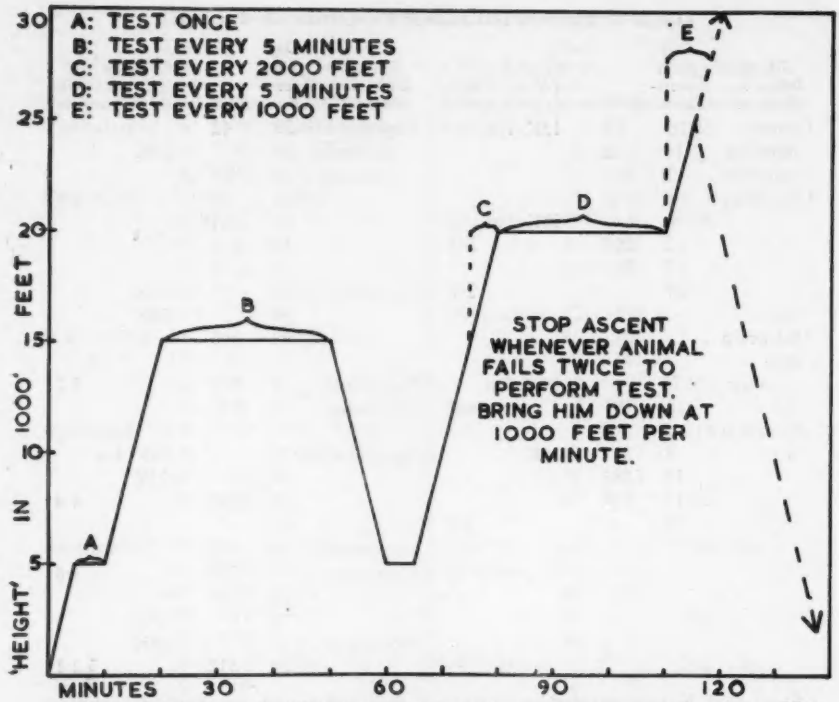

Fig. 14.—Pattern of "flight" used in the large low pressure chamber. Note that thirty minutes are spent at 15,000 feet, and again at 20,000 feet.

readily arrest respiration, tending to breathe fairly steadily through her various aggressive activities. Respiration was arrested during brief periods of apprehension, however, as when a glove was held in a threatening attitude above her head. From a tin of food and metal objects presented to her she unhesitatingly picked out all the peanuts and stuffed them unpeeled into her food pouches. At a suitable moment she took them out singly, peeled, and ate them. (This seems a natural response, but in fact is the most intelligent method any animal showed in the chair. Usually the animal was so agitated that it fumbled the process somewhere.)

There was a mild right spastic hemiparesis, with a grasp reflex in the hand.

During testing in the small chamber (*see below*) death occurred in a severe asthmatic attack at 6,000 feet. No sign of disease was present on macroscopic examination of the internal organs. Portions of the lungs were sectioned, and the histological report by Dr. W. Thomas Smith concludes:

FIG. 15 (a).

[*For captions see p.* 474]

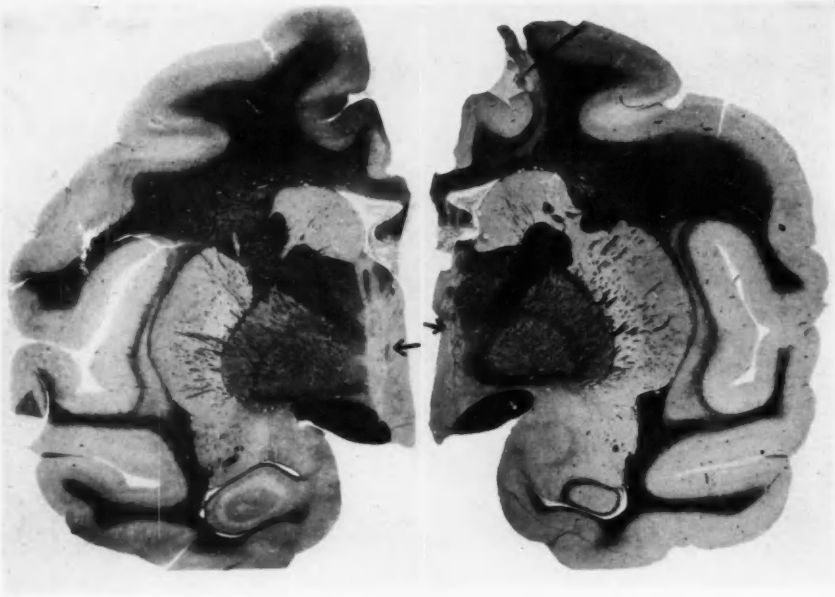

FIG. 15 (b).

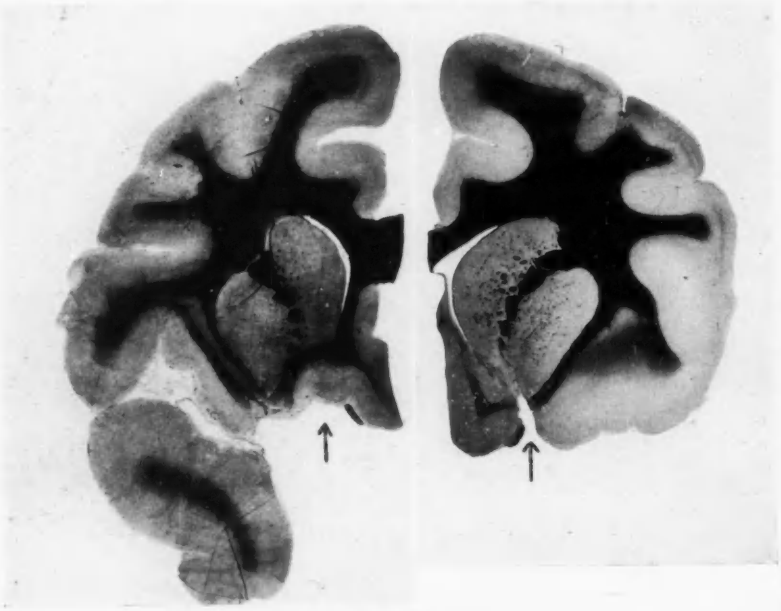

FIG. 15 (c).

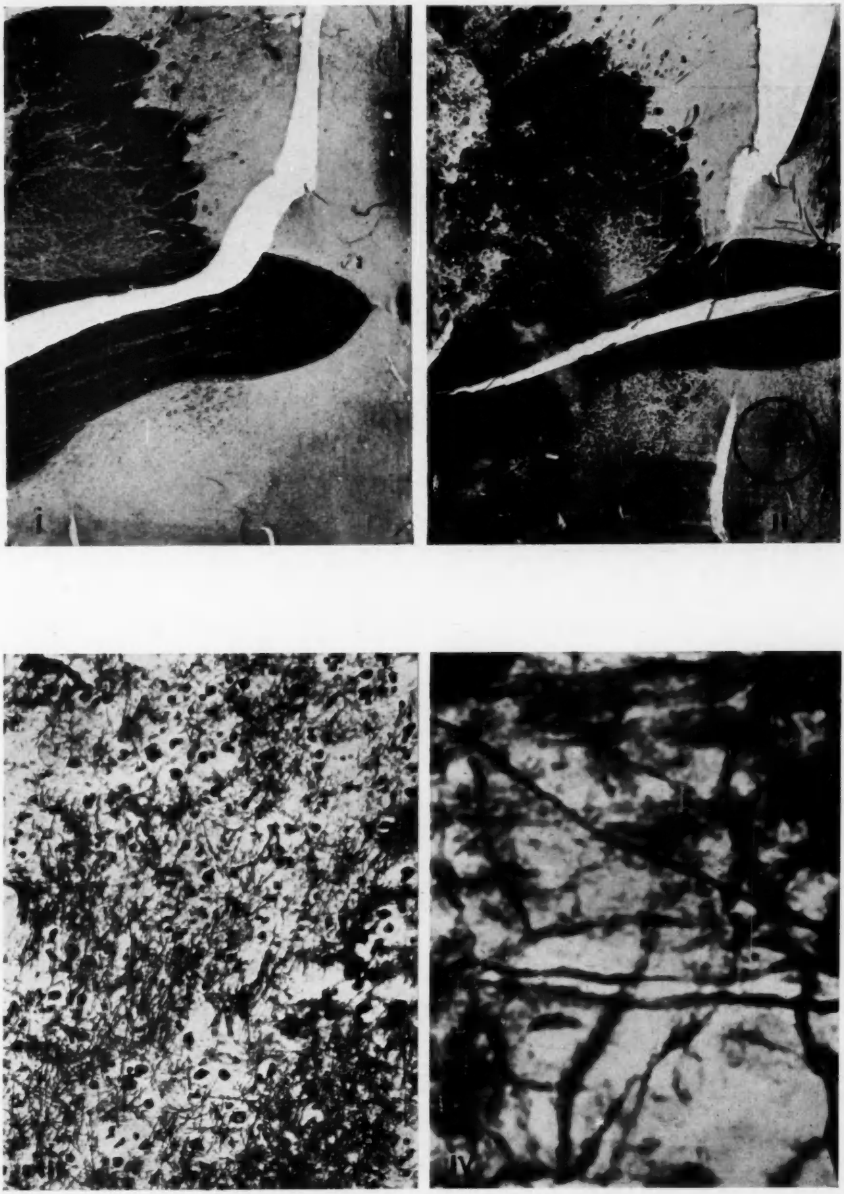

FIG. 15 (d).

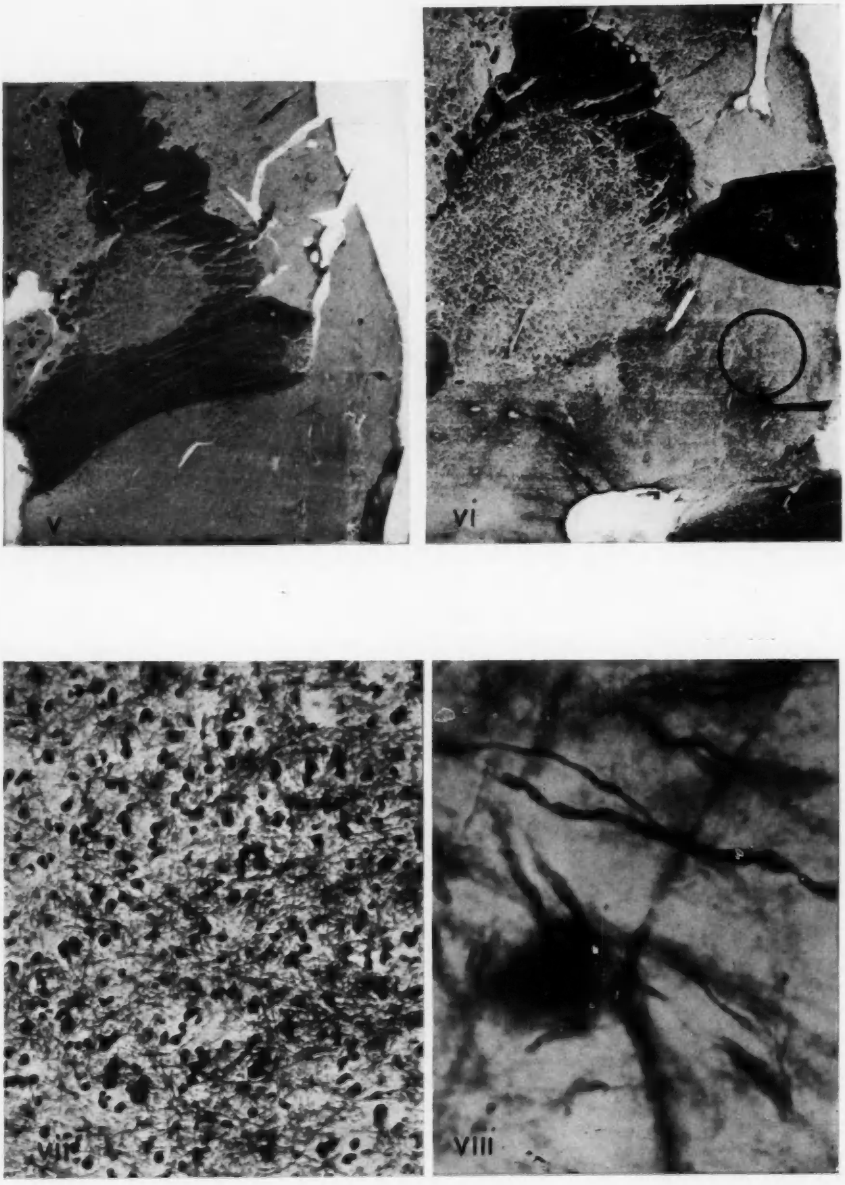

FIG. 15 (d) (*contd.*).

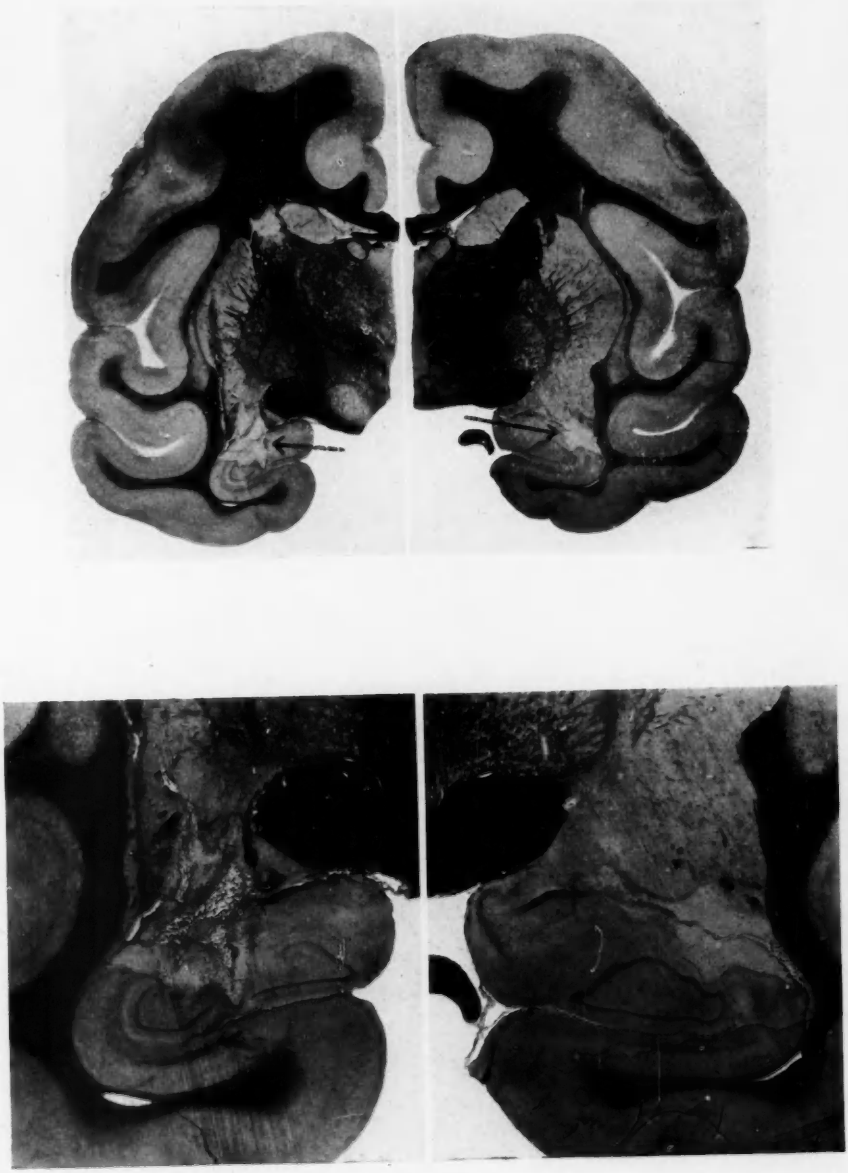

FIG. 16 (a).

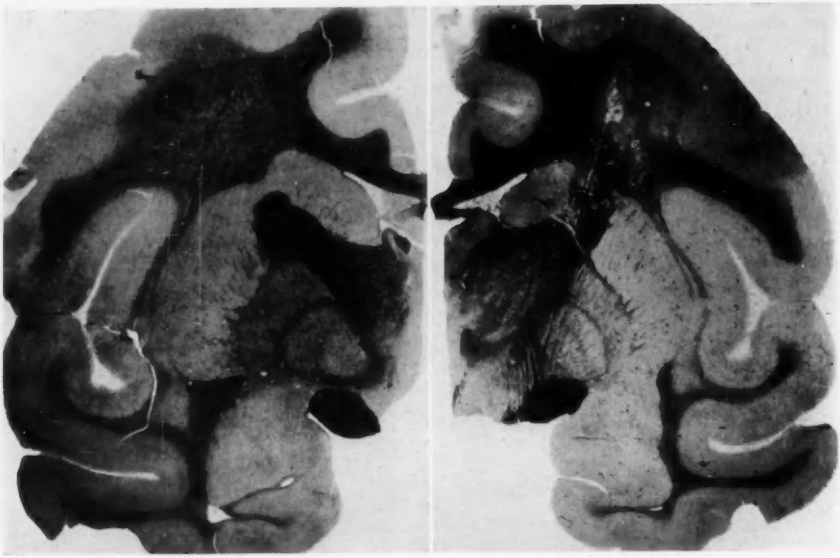

FIG. 16 (b).

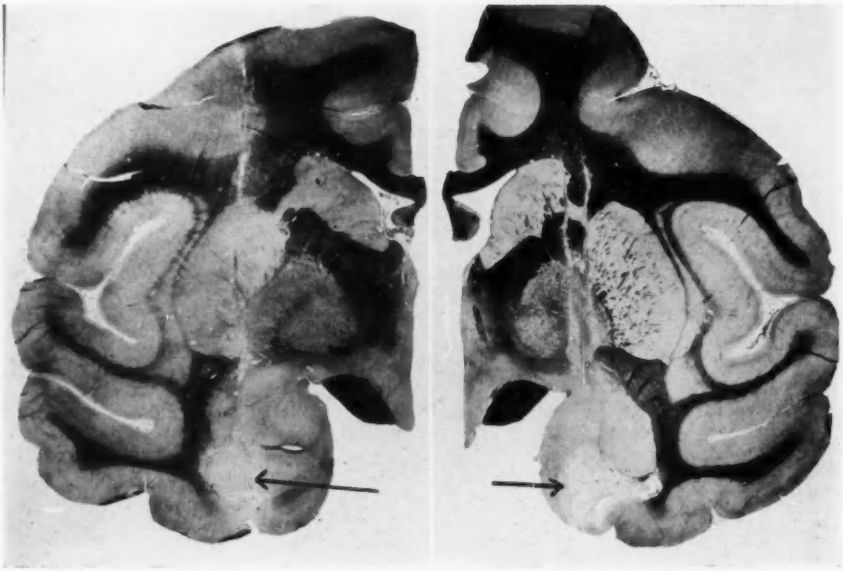

FIG. 16 (c).

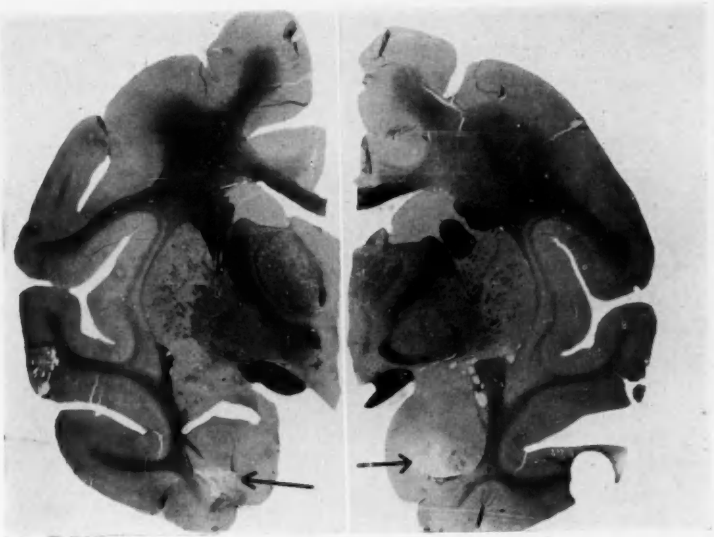

FIG. 16 (d).

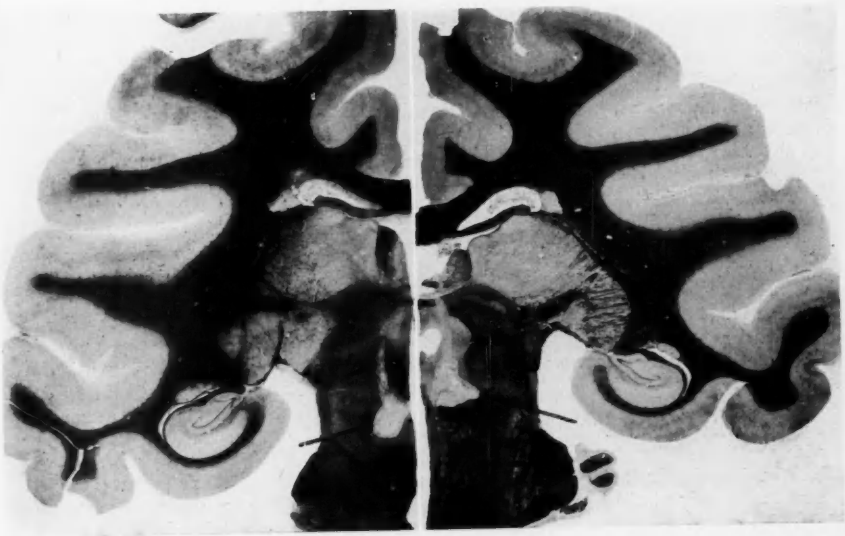

FIG. 17 (a).

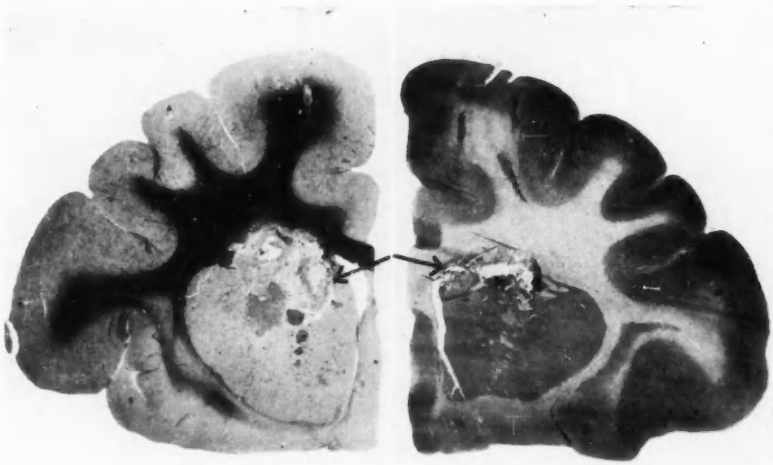

FIG. 17 (b).

LEGENDS FOR FIGS. 15, 16, 17

Fig. 15.—(a) Sections through lesions in "Prethal. 3"—No. 2659 (*see text*) Myelin stain: celloidin. (b) Section through lesion in first animal with lesions in "prethalamic bundles" ("Prethal. 1"). Myelin stain: celloidin. (c) Lesions in "Area 13". In the left hemisphere there is damage to the inferior tip of junction between caudate and putamen, but there is no degeneration of the caudate head. In each case the olfactory tract is intact. (d) Sections in increasing magnification of region of prethalamic bundle in normal and in right hemisphere of "Prethal. 2." (Frozen sections.) (i) Myelin stain of normal brain in this region to show that no substantial number of myelinated fibres runs in the region in question. (ii) Frozen section of normal brain to show that unmyelinated fibres do run in the region. They are especially numerous within the circle outlined in black. (Glees silver stain for unmyelinated fibres.) (iii) High power of area within circle shown in (ii). (iv) Same as (iii) under oil immersion. (v) Myelin stain to show destructive lesion in "Prethal. 2." Destruction of cells is present below as well as above the anterior commissure (*see below*). (vi) Silver-stained section of "Prethal. 2." Unmyelinated fibres are much less numerous than in (ii). Section is at level of optic chiasma, i.e., just behind the lesion. (vii) High power of area within circle shown in (vi). (viii) Same as (vii) under oil immersion. Unmyelinated fibres are less numerous, and less clear in outline than in (iv) and show irregularities in density of staining, with the "beaded" appearance of degenerating fibres.

Fig. 16.—(a) Lesions in amygdaloid region (Amygd. 1). This animal was rendered extremely placid (*see text*). The lesions are seen to be posterior to the amygdaloid nucleus, affecting principally the junction between the tail of the caudate and the putamen. Fibre tracts probably destroyed are the stria terminalis, the temporo-pontine tract running backwards over the lateral geniculate body to the

peduncle, and fibres running medially towards the ansa lenticularis. This section is at the maximum dimensions of the lesions. Before destruction, stimulation produced apnœa from these points. (b) Section through amygdaloid nuclei in Amygd. 1. There is practically no damage here. (c) Lesions in animal Amygd. 2. This animal was rendered moderately placid: the lesions are within the basal parts of the amygdaloid nucleus and pyriform cortex. At the time of operation the anæsthesia was too deep, and no effect could be obtained from stimulation. (d) Lesions in animal Amygd. 3. This animal was least affected in its behavioural reactions: the lesions are nicely placed within the basal parts of the amygdaloid nucleus. Stimulation at operation caused apnœa at these points.

Fig. 17.—(a) Lesions in mid-brain reticulum just ventro-lateral to the central grey. Apnœa was produced by stimulation of these points during operation. (b) Lesions in caudate nuclei (Caud 3). The section from the right hemisphere is stained for myelin, that from the left for cells.

". . . In the main bronchus the epithelial goblet cells are distended and the submucosa is infiltrated with round cells and occasional eosinophiles. Both lobes show diffuse hyperæmia and focal areas of collapse which are situated mainly in relation to small bronchioles. Many bronchioles contain mucoid secretion and cellular debris. The tissue between the collapsed areas shows compensatory emphysema and a few interstitial aggregates of lymphocytes and plasma cells. There is no evidence of œdema or infection.

" The above changes are less extensive than, but in most other respects similar to, the lesions usually found in the lungs in fatal cases of human asthma."

Area 13 (fig. 15c).—The animal in which Area 13 was ablated had bilateral lesions made in one operation. Two days later he began to have repeated focal fits affecting the left side of the body. These were controlled by paraldehyde, but during the following three days he had a left hemiparesis and required tube-feeding as he did not chew or swallow properly. Twelve days after the operation he began to eat for the first time. He was still ataxic, particularly in the upper limbs.

Even at this stage he was very aggressive, rushing at the observer, striking out and attempting to bite with a sideways toss of the head to the left. Post-operatively he had also an extremely red face, which with the aggressive behaviour gave him an appearance of undignified rage, which caused him to be named " The Colonel." He was sacrificed seven weeks after operation.

The " Amygdaloid " Group (fig. 16).—This group is of considerable interest, not so much because of any elucidation of the function of the amygdaloid nucleus, but because it suggests that this region should be considered in a broader way than has been done on some occasions. All 3 animals might be considered to have some alteration in " temperament,"

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in that after operation even the least affected would accept food from the hand without grabbing and darting away. However, one animal was so little altered that it could readily pass for normal: another was rendered placid, but only moderately so. These animals had lesions nicely placed in the amygdaloid nucleus. The third animal had bilateral lesions postero-lateral to the amygdaloid nucleus, in the junction between the tail of the caudate nucleus and the putamen. Known fibre tracts destroyed include the stria terminalis, part of the temporo-pontine tract, and fibres passing medially towards the ansa lenticularis. This animal, although the lesions were small, was completely changed in temperament.

She recovered consciousness quickly, with some shivering, but remained drowsy for another twenty-four hours. Thereafter it was noted that she would crawl deliberately out of her cage, disregarding the presence of a human being, and for the most part would lie passively when held, without any sign of either pleasure or aggression—like a schizoid, "detached from her surroundings."

During the next few days she dozed a lot; when left alone in the activity-testing cage she cried plaintively. She was noted to be visually very inquisitive, peering around corners, and moving to see what was going on in any part of the room. She did not, on the other hand, pay much attention to sounds or to touch. Although with the passage of time the extreme placidity diminished, she remained, until her sacrifice over four months later, a "changed woman." From a slim, quick, apprehensive, extremely active creature, she became placid and fond of eating. A mild right hemiparesis cleared up in a month. Both before and after operation she was intelligent, as shown by her swift learning of conditioned reactions in test situations. The only act that would produce a wild reaction of screaming and pawing and lashing of limbs was to cover her eyes with a glove. Loud sounds, sudden advances, or unexpected pin-pricks produced no such effect.

Although she did not phonate often, she had a wide range of phonation —screams, gutturals and a plaintive "Oooh." Her posture was normal.

Of the other two animals, the "tamer" one showed some visual curiosity, while in the other, although actions of aggression or apprehension were present, there was no obvious arrest of respiration during them, except when he was actually phonating.

Other groups.—Animals with lesions in the subthalamus, centromedian nucleus of thalamus and mid-brain reticulum showed various features, some identical with caudate, amygdaloid or prethalamic lesions, others

not: e.g. placidity, myoclonic jerks, tremor, ataxia; and in the "mid-brain" animal, excitability and an inordinate appetite.

Small Chamber Experiments

In order to investigate the nature of the change which allowed certain animals to resist anoxia better after operation than they had done before it five animals were exposed to anoxia in a small chamber in which they were confined with electrodes strapped to the skin by gauze soaked in collodion. By this means an electrocardiogram was taken continuously throughout the experiment, and the respiratory rate and depth were also recorded by means of the changes in capacity of the body between two flank electrodes. The "flights" were replicas of those in the large chamber in which the anoxic "ceiling" was known, so that it was possible to

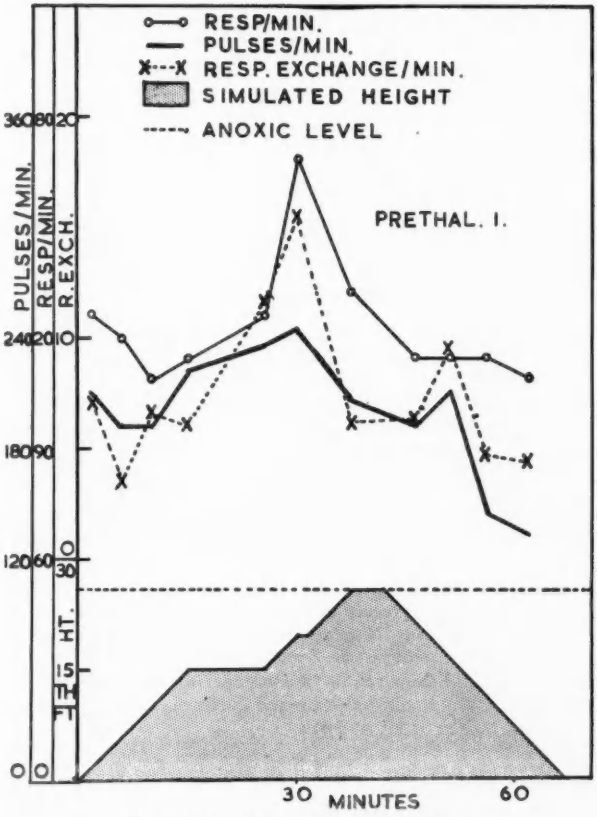

Fig. 18 (a). *(See captions next page.)*

compare respiratory and cardiac function with the known responses of the whole animal, with the reservation that in the small chamber the animal was necessarily kept still during the whole experiment by confinement in a frame which allowed only minimal movements of head and limbs. Samples of the results are shown graphically in figs. 18–20. It is seen that as the anoxic level is approached the normal animal has a rise in respiratory rate and exchange but just as the anoxic level is reached the exchange falls. (The rate may or may not fall.) By contrast with this is the post-operative record of the "prethalamic" animal (P.M.8), which

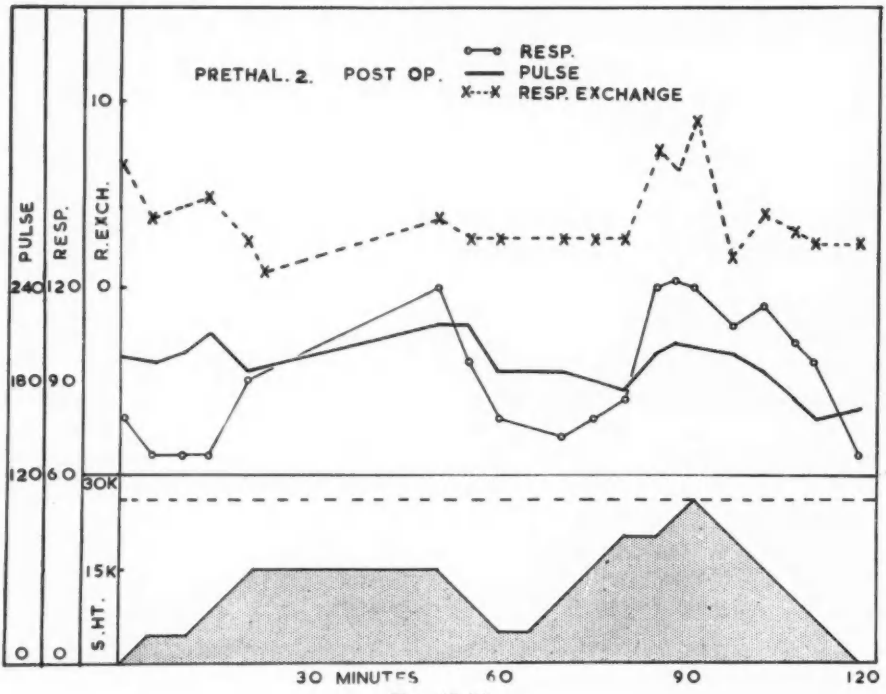

FIG. 18 (b).

Fig. 18.—(a) Pre-operative record of first "prethalamic" animal to show a typical record in an unoperated case. Note the fall in respiratory rate and exchange and pulse-rate just before decompensation occurs. (b) Record of second "prethalamic" animal after operation, to show results in a case where resistance to anoxia had been increased. Note that the respiratory rate and exchange and pulse-rate reflect faithfully the simulated height at all stages.

had an increase in resistance to anoxia. In this animal the respiratory rate reflected faithfully the degree of anoxia, and as the anoxic level was

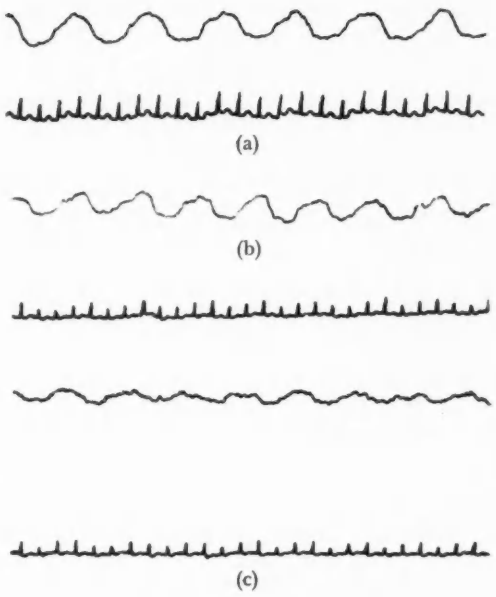

Fig. 19.—Respiratory and electrocardiographic records in an animal with bilateral lesions in the caudate head (Caud. 1). (a) At "sea level." (b) On reaching "20,000 feet." (c) "20,000 feet" after five minutes. (This was the "ceiling" of this animal.) Note the depression in respiratory excursion just at the level where anoxia causes failure of function.

reached there was no fall in either the rate or exchange, but instead a rise in both. There were, however, profound changes in the electrocardiograph.

One possible explanation of the phenomenon seems to be that hyperpnœa due to anoxia is normally counteracted by lowering of CO_2 pressure with resultant hypopnœa, and that the animal with the "prethalamic" lesion was no longer so responsive to the lowering of this CO_2 pressure. Since the fibres were destroyed because they carried an apneustic effect, this idea may not be unreasonable. It would suggest that Area 13, whatever other functions it may have, acts as one of the highest centres for a system which regulates CO_2 by means of control of respiration. (Unfortunately one of the other animals with similar lesions, (P.M.3), developed pulmonary tuberculosis, and the other died in the small chamber of an attack of asthma (P.M.11).) Mild anoxia in the early and late stages of the "flight" caused a general lowering of respiratory rate and exchange. In the whole series the pulse rates showed no consistent change, but mild alterations in the form of the electrocardiograph were seen, e.g. reversal

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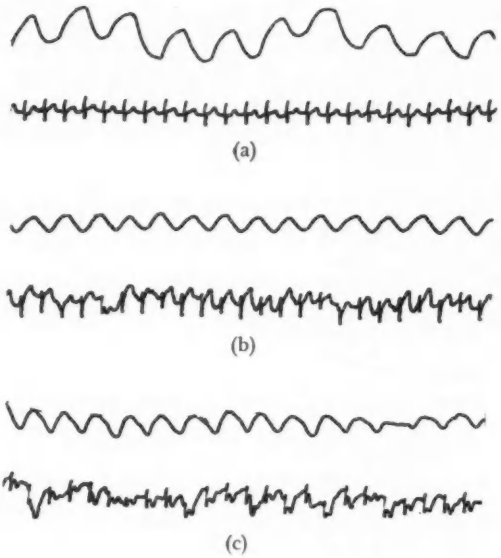

Fig. 20.—Similar records in animal after bilateral lesions in the "prethalamic bundles" (Prethal. 2.). (a) At "sea level." (b) At "20,000 feet." (c) At "26,000 feet." (The "ceiling" had risen to 28,000 feet in this animal.) Note that the smaller diminution in respiratory excursion is more than compensated for by the increase in respiratory rate. The electrocardiogram becomes in the later records more abnormal than in 20(a). It is possible that unmodified alkalæmia has had a toxic effect on the heart.

of Q.R.S., while bradycardia was common during the "descent." The more profound changes in the electrocardiograph in the animal rendered resistant to anoxia might suggest that a protective mechanism had been damaged or destroyed.

Discussion

Although the original aim of the series of experiments was to elucidate certain problems which had arisen regarding hyperkinesis on the one hand and respiratory control on the other, it was soon apparent that previous information concerning cerebral control of respiration was so fragmentary that a large section of the work had to be devoted to laying a foundation of knowledge concerning the pathways by which respiratory effects of cortical stimulation were carried to the brain-stem. This became a major task in itself. It was no disadvantage that such pathways were investigated primarily in terms of co-ordinates in the Horsley Clarke planes, as this was the form in which the information had to be used. Correlation of

the data with possible anatomical structures was a by-product of this part of the investigation.

Three types of descending system emerged. One was the stria medullaris, habenular nucleus and habenulo-peduncular tract for a certain part of its path in the reticular substance of the mid-brain. This system produced, on mild stimulation, violent expiratory movements; on stronger stimulation, apnœa in expiration. It seemed feasible that these structures represented one system which was concerned in olfactory or, more broadly, in nasopharyngeal reflexes.

Another system included some point in or near the amygdala. Experimental results were not conclusive, but suggested that descending pathways from this point passed not only through primitive tracts in the subthalamus towards the mid-brain, but also through the newer cerebral peduncles as far as the pons. In addition to these two systems, points were found in several structures which produced profound apnœa when stimulated. Such structures included various thalamic nuclei, and the subthalamus, but no information concerning the reason for the apneustic effects emerged from the work under discussion.

The last system was the posterior orbital gyrus (Area 13), with its descending pathways. The descending tract seemed to be single as far back as the anterior limit of the thalamus, after which it was represented both in the subthalamus and in the cerebral peduncle as far as the rostrolateral aspect of the pons. Caudal to this last point only the reticular substance could produce the apneustic effect.

Considerable attention was devoted to the last system, and the series of chronic experiments was designed to throw light on the possible significance of it. It seems clear that Davis's proposition has been confirmed that hyperkinesis after ablation of Area 13 is profound only if the striatum has been damaged either directly or by ischæmia. The attempt on the other hand to demonstrate a true respiratory deficit in those animals which have lesions only in Area 13, or in the tracts descending from it, has met with the, at first surprising, result that the resistance to anoxia is increased. This observation is not true of the animals which have lesions in the striatum alone, so that the converse of Davis's proposition is also true in that respiratory disturbances are observable only if tracts descending from Area 13 are damaged. Further investigations into the precise nature of the respiratory disturbance suggest that it is due to a removal of some inhibition to hyperpnœa when the animal is subjected to low gaseous pressures. It is propounded that this inhibition is that produced by alkalæmia from lowering of CO_2 pressure in the alveoli and blood. Whether the mechanism is a direct one in the cortex or an indirect one

via chemoreceptors supplying afferent stimuli via the vagus nerve is not clear. In view of the demonstration by Bailey and Bremer (1938) of some connexion between the central end of the vagus and electrical potentials in Area 13 the latter possibility gains some strength.

The implications of knowledge concerning cerebral control of respiration gain deeper significance when it is remembered that every significant change of emotional tone is heralded by a change in respiratory rhythm. If the material is examined in this respect it is seen that all of the structures here studied fall within that broad system which has been given prominence as being developmentally the rhinencephalon, but seems in higher forms to be at least as closely connected with temperament and emotional tone. Its claim to functional unity depends on the demonstration of the histological uniformity of its cortical components (the allocortex of Bailey and von Bonin, 1951), interconnexions between component parts of the system as demonstrated by strychnine neuronography (Pribram, Lennox and Dunsmore, 1950), and the similarity of effects of stimulation or ablation of various parts of the system, in that all bear closely on the outward manifestations of emotion or "temperament." (Smith, 1941, 1945; Klüver and Bucy, 1939; Ward, 1948; Fulton and Ingraham, 1929). The exact rôle of the "rhinencephalon" has been suggested as a non-specific activator of other cerebral functions (Herrick, 1933), as a mechanism for prolonging emotional states (Papez, 1937), and as a cortical representation of the viscera—a "visceral brain" (MacLean, 1949, 1952). In a critique of the experimental work done on this system, the author has suggested that the name "Thymencephalon" is justified denoting the affective or temperamental part of the brain (Turner, 1953).

The observations on the animals in the present study reveal two clearly defined groups which show disturbances of temperament. The first group comprises those animals with lesions in Area 13 or in its descending tracts. Two out of four of these are noted as being particularly irascible after operation, and the irascibility has been accompanied by redness of the face, due to dilatation of the small blood vessels, particularly those of the nose and the surrounding parts of the cheeks. A third animal of the group is noted to have had asthma after operation, exacerbated especially by emotional disturbances. Having died during a "'flying" experiment at only "6,000 feet," it has had the asthmatic changes in the lungs confirmed histologically.

It is of interest that Fulton and Ingraham (1929) found that bilateral lesions in the orbital cortex of cats produced chronic lowering of the threshold of rage reactions. Their lesions must have been very close to the structures discussed here.

If it is true that Area 13 and its descending pathways represent a cortico-medullary system which may be concerned with, among other things, the control of CO_2 in the blood by means of alterations in respiratory rate and exchange, it is apposite to remark that unchecked disturbances of mood have resulted in human patients whenever serum potassium levels lie outside of certain mean values (Hawkins *et al.*, 1951; Richardson *et al.*, 1953).

The second group of animals showing changes in temperament is the " amygdaloid " group. Of three animals one has shown changes so marked that its placidity has far exceeded that seen in any normal healthy animal not tamed in babyhood. This represents not only a change from a pre-operative observation, but an abnormality in terms of species. It is therefore of particular importance that the lesions in this animal involve not the amygdaloid nucleus but the junction between the caudate tail and the putamen, with, it is suggested, fibres flowing caudally from temporal lobe structures to join the medial fore-brain bundle, subthalamus, and cerebral peduncle.

Of the other two animals one has been unchanged in temperament, and one rendered temporarily slightly more placid than normal. In these the lesions have been placed accurately inside the amygdaloid nucleus.

Profound temperamental changes have been described in rhesus monkeys after temporal lobectomy by Brown and Schafer (1888), and Klüver and Bucy (1939). These include abolition of all outward evidence of the emotions of anger and fear in behaviour and in vocal and facial expressions; "psychic blindness"; strong tendencies towards oral examination of objects; excessive reaction to all visual stimuli; excessive and abnormally diverse sexual behaviour; and a change in dietary habits. The animals of the present series show only the emotional " bleaching," and an increase in visual curiosity. The most profoundly affected animal has not shown any of the other changes, but with regard to sexual behaviour, changes have been observed by Klüver and Bucy particularly in males, while this animal is female.

The complete temporal lobectomy involves removal of many structures. The importance of the present observations is that the lesions are tiny. Of small lesions Klüver (1951) says, "Our own experiments merely indicate that partial removal of this region (hippocampus) leads to a transitory appearance of some of the symptoms." Nevertheless it seems that further knowledge must emerge now from correlation of the results on numerous animals of small lesions carefully applied, and exactly symmetrical. This remains to be done.

It is probable that knowledge of the neurophysiology of this part of the

brain will be of prime importance to surgeons contemplating operations for "temporal lobe epilepsy," or for mental illnesses involving uncontrollable aggression, fear or anguish. Attempts at operation have been made where these emotions accompany auditory or visual hallucinations (Freeman and Williams, 1952; Obrador, 1947) but there is no indication from animal experimental work that hallucinations need be concerned in the syndrome in which such operations may give benefit. Uncontrollable rage or fear leading to misery and distress on the part of a psychotic patient would appear to be the indication for such intervention, and the target appears to be the region of the junction between the tail of the caudate nucleus and the putamen at the anterior end of the temporal horn of the lateral ventricle.

Summary

In series of acute and chronic experiments on 34 rhesus monkeys control of respiration by certain cerebral structures has been investigated, together with the phenomena of hyperkinesis. Temperamental changes have been noted carefully in conjunction with all the experiments. The following conclusions have been reached:

(1) The cortex of Area 13 (Walker) has a controlling effect on respiration, as has been found previously.

(2) This effect may have some connexion with CO_2 level in the blood, and possibly with damping of rage reactions.

(3) The effects on respiration are carried downwards by a bifid pathway to the reticulum of the pontine brain-stem. The caudate nucleus does not appear to be involved in this pathway.

(4) The impression that hyperkinesis results from damage to the head of the caudate nucleus and not from damage to Area 13 or its descending pathways is confirmed.

(5) Temperamental changes towards placidity may result not so much from damage to the amygdaloid nucleus as to the junction of the tail of the caudate and putamen, where fibres pass from temporal lobe structures towards the medial fore-brain bundle, the subthalamus, and the cerebral peduncle.

(6) Numerous other cerebral structures have some controlling effect on respiration as part of, or as an accompaniment to, their own functions. Information about these is given in the various sections of the paper.

(7) The subject matter of the experiments is discussed in the light of recent views upon the rhinencephalon.

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Notices of Recent Publications

Cytoarchitecture of the Human Brain-Stem. By Jerzy Olszewski and Donald Baxter. 1954. Pp. 199. 42 Plates and numerous illustrations. Published by S. Karger, Basel and New York. Price 72.80 fr.

This fine photomicrographic atlas comprises the third of a series prepared by Dr. Olszewski and his collaborators. The first two volumes, concerning the thalamus of the macaque monkey and the brain-stem of the rabbit, were specifically prepared for anatomical reference in experimental studies. For this purpose they have proved to be of very great value, particularly in the investigation of the functional significance of local regions which are not easily defined by clear-cut anatomical boundaries. The present volume is intended for reference in neuropathological studies. As Dr. Greenfield emphasizes in the Foreword, the very intricate nature of the cytoarchitecture of the human brain-stem—and particularly of those diffuse collections of cells which are commonly grouped under the heading of the "reticular formation"—always poses a most serious problem to the neuropathologist who is concerned to map the extent of pathological lesions affecting this part of the brain and to attempt a correlation of disorders of function with the distribution of structural changes. With the increasing attention which is now being directed to the functional significance of this reticular formation in cerebral activity as a whole, the need for an accurate atlas of the human brain-stem has become very pressing indeed.

Nothing but praise can be expressed for the microphotographs which form this atlas. The Nissl sections are all wellnigh perfect, and each local group of cells, or diffuse collection of cells, is represented not only by photographs at low magnification which illustrate their general topographical arrangement, but also by photographs at high magnification to demonstrate cytological characteristics. The photographs are accompanied by short descriptive commentaries, with brief references to evidence for the fibre connections of cellular aggregations, so far as these are known, and to the experimental evidence of their functional significance. For the neuro-anatomist, as well as the neuropathologist, this superb atlas is of quite first-class importance. W. E. Le G. C.

Some Problems in Neurophysiology. By F. Bremer. 1953. Pp. 79, illus. 32. Constable Ltd., London. Price 21s. net.

The best of these three lectures is undoubtely the last, an excellent summary of the present position of our knowledge of the auditory cortex. Bremer's early experiments on clicks laid the foundations of our knowledge of the auditory centre. Clicks have the advantage that they are unlikely to have any special significance for the animal, but they contain a very wide range of frequencies, and ultimately more refined techniques involving the stimulation of small parts of the basilar membrane or the use of pure tones near threshold were necessary to study the localization of sound within the auditory centre. There is also an interesting discussion of the puzzling question of II and III auditory areas. One at least seems to be secondary in the sense that its impulses have been relayed from the primary area. In the secondary visual areas there seem to be important species differences. Though

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Marshall and Talbot find a minor image visual area II in the rabbit, there is no sign of it in the monkey. Bremer remarks on the species differences in the amount of overlap in the primary areas. It would be interesting to know if there are corresponding species differences for the secondary auditory areas.

The second chapter on the E. E. G. is largely an account of Bremer's pioneer work on "tonus cortical" and sleep and its development and modification by Magoun and Moruzzi, and by Jasper. This subject is of great topical interest and the growth of our knowledge is clearly displayed.

The first chapter is the weakest in the book. It deals with synaptic transmission, inhibition and autorhythmicity in the spinal cord. As those lectures were given in 1950, this material is largely out of date. This is, however, the author's bad luck and a supplement has been added to bring the book up to date. There is also an attack on the idea of reverberatory chains of neurones and a fervid plea for the concept of neuronal autorhythmicity. The evidence for neuronal autorhythmicity in any rigorous sense is nowhere stated, and the two concepts are not mutually exclusive. Lorente de No's hypothesis is dismissed with the words "there is an unavoidable factor of subjective interpretation and arbitrary choice in the deduction of central wiring diagrams from stained sections of the grey matter network." Perhaps the main value of this chapter is the reminder that we have still very little exact knowledge of the organization and behaviour of cortical neurones.

D. W.

Hypnotism. By ANDRÉ M. WEITZENHOFFER. 1953. Pp. 380. Chapman and Hall, Ltd., London. Price 48s.

In my article on "Hypnotism" in the *British Encyclopædia of Medical Practice* I defined hypnosis as a suggestively induced state of hyper-suggestibility. I concluded the section on the history of hypnotism in the following words: ..."in strict truth, little more is known now about the true nature of hypnotic phenomena than when Mesmer in his violet silk robe wandered through the Paris salons touching hysterical countesses with his magnetic wand."

After reading Mr. Weitzenhoffer's book, I have little reason to revise this opinion.

The book is a praiseworthy and honest attempt to summarize the data provided by experimental psychology and physiology in relation to hypnotic phenomena. As such, it is a very welcome addition to the serious literature on the subject It would be too much to expect that all the relevant literature should receive mention; but it is a little hard to understand why there is no specific mention of Salter's work, seeing that Salter, also an American, has made studies in the same field and come forward with a clear-cut (if highly controversial) theory of hypnosis based on Pavlov's conception of conditioned reflexes.

Although Schultz's name is mentioned on various pages, there is no account of his "Autogenes Training," a system which does open up interesting speculations as to the possible nature of the hypnotic state. A similar omission is the lack of reference to Kretschmer's "Active Fractional Hypnosis." In view of these lacunæ, it is not surprising that Yoga comes in for no special treatment.

It is perfectly true that Mr. Weitzenhoffer purposely refrains from dealing with hypnosis in its more clinical aspects; but all the above-mentioned contributions have their theoretical aspects as well.

Mr Weitzenhoffer comes to the conclusion that the differences between hypnotic and waking phenomena are essentially quantitative, not qualitative, that all the phenomena connected with suggestibility do not result from a single process but from processes of different origins.

These findings are perhaps somewhat vague and negative. However, more or less

in the words of the "blurb" on the dust-cover, they do serve to separate myth from actuality and to screen empirically established knowledge in the many unfounded beliefs concerning the subject.

For some time to come, this book will serve as a sheet-anchor for research workers in the field of hypnosis; and it is to be hoped that many more psychologists, neurophysiologists and clinicians, with a really adequate scientific training, will occupy themselves with the task of illuminating further this still obscure and very important problem.

E. B. S.

The Course of Disseminated Sclerosis. By PAUL THYGESEN. 1953. Pp. 268. Figs. 25. Rosenkilde and Bagger, Copenhagen. Price in U.K. 25s.

This monograph is intended "to give a close-up of the course of disseminated sclerosis." Sixty patients were followed for an average period of 18·3 months. One hundred and five "attacks" were studied. The longest observation period was twenty-eight months. The average duration of illness before special observation was eight years.

The author gives a careful and extensive record of facts associated with his group of patients, and attempts to answer some of the questions which arise each time a neurologist sees a case of disseminated sclerosis, particularly in regard to prognosis and the efficacy of treatment. He believes "that the exceptional position of optic-nerve lesions with the symptomatology of disseminated sclerosis exists more by tradition than by statistical foundation, probably due primarily to the high qualification attributed by us—and the patients—to visual power."

The monograph is valuable in its description of the whole range of symptoms of the disease, but it does not convincingly suggest to the reader that significantly new facts have emerged.

The translation is so bad as to make the work almost unreadable. A dozen or more corrections per page are often required, and the constant struggle for meaning is exhausting. Examples may be given in "deteriorates the prognosis," "appreciable violation of the patients' histories," "fortuitous period of their disease."

W. G.